University of Alberta

Enantioselective Lewis Acid-Catalyzed Allylboration of Aldehydes Using Camphor-Derived Diols: Development and Synthetic Applications.

by

Hugo Lachance ©

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy

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Abstract

Aldehyde allylboration chemistry has been an essential tool in organic synthesis for many decades. Even though many methods are available, none of them possesses all of the desired attributes. One would hope to develop a method that would be general, provide consistently high yield and selectivity, be compatible with a wide range of substrates, easy to perform, environmentally friendly, and catalytic. In the course of our studies on the Lewis acid-catalyzed allylboration of aldehydes, we found that the use of a camphor-derived chiral auxiliary in conjunction with $Sc(OTf)_3$ provided us with allylic boronate reagents that are stable to purification by silica gel and could be manipulated without particular precaution. These reagents afforded the desired homoallylic alcohols in good yield and excellent enantioselectivity. Chapter 2 describes our work in the development and optimization of this new catalytic method for the allylboration reaction.

The successful application of the camphor-derived diols in this reaction justified our investigation into the development of new preparations of this chiral auxiliary. The two new syntheses of the desired diol are described in Chapter 3. The first approach was executed in two steps from camphorquinone in 55%

overall yield and purified by a single final recrystallization. The second route made use of simple camphor as starting material, and provided the final diol in four steps in 55% overall yield and required only a recrystallization for purification after the final step.

The generality of the catalytic conditions was tested in its application to the additions of α-silyl substituted allylic boronates described in Chapter 4. Unfortunately, under the catalytic manifold, this class of boronates provided either the allylsilation product or an unseparable mixture of products.

Finally, Chapter 5 presents our work towards the synthesis of psymberin using our Lewis acid-catalyzed allylboration of aldehydes. The application of the Lewis acid-catalyzed allylboration allowed us to prepare the desired homoallylic alcohol resulting from the reaction between a methallylboronate and D-(*R*)-glyceraldehyde acetonide in 75% yield as a single diastereoisomer. An advanced intermediate containing the pyran core was also obtained through the tandem IEDHDA/allylboration reaction in 50% yield and good enantioselectivity (86%).

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Throughout the past five years many people have crossed my path in research as well as in my personal life. Much of the work described in this thesis would not have been possible without many of them.

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This thesis is the result of five years, most of which were spent doing laboratory work. Over the years, the quality of the people I rubbed shoulders with everyday has been extraordinary. I want to thank all the group members, past and present, and in particular Michel Gravel, Xiaosong Lu, Miguel St-Onge, and Lisa Carosi whit who I collaborated at one point or another in my research.

Special thanks goes to the people who spent some of their precious time to proofread my thesis, Tim Elford, Marlin Penner, Lisa Carosi, Vivek Rauniyar, Sam Mothana, Marie Bérubé, Olivier Marion, and Duane Stones. Each of them contributed in their own way to make my thesis what it is today.

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En terminant, je voudrais remercier les gens plus près de moi, tout spécialement ma femme Julie et celle qui est ma plus grande réussite des cinq dernières années, Alice. Je voudrais aussi remercier mes parents, Nicole et Louis pour leur support durant mes etudes et lors de mes voyages au Québec. Merci à toute ma famille (Charles, Karine, Dany et les autres) et à ma belle famille.

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List of Abbreviations

Ac	Acetate
Adm	Adamantyl
Bn	Benzyl
Bp	Boiling point
Bu	Buthyl
Bz	Benzoate
CNS	Central nervous system
conv.	Conversion
d.e.	Diastereomeric excess
d.r.	Diastereoisomeric ratio
dba	Dibenzylideneacetone
DEIPS	Diethylisopropylsilyl
DIBAL	Diisobuthyl aluminium hydride
DMDO	Dimethyldioxirane
DMF	Dimethylformamide
DMS	Dimethylsulfide
DMSO	Dimethyl sulfoxide
e.r.	Enantiomeric ratio
ee	Enantioselectivity
EI	Electron impact

equiv	Equivalent
ES	Electro spray
Et	Ethyl
fod	Tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate
GI_{50}	Growth inhibition 50%
HMPA	Hexamethylphosphoramide
HRMS	High resolution mass spectroscopy
IEDHDA	Inverse-electron-demand-hetero-Diels-Alder
Ipc	Isopinocampheyl
i-Pr	Isopropyl
IR	Infrared
LDA	Lithium diisopropylamide
m-CPBA	*meta*-Chloroperbenzoic acid
Me	Methyl
MEM	2-Methoxyethoxymethyl
MO	Molecular orbital
Mp	Melting point
NMR	Nuclear magnetic resonance
Nu	Nucleophile

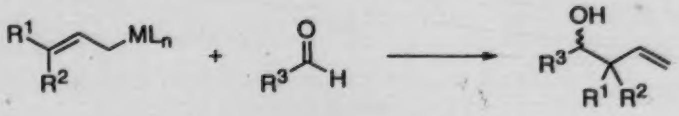
OTf	Trifluoromethane sulfonate
Pg	Protecting group
Ph	Phenyl
PMB	*para*-Methoxybenzyl
PPTS	Pyridine *para*-toluene sulfonate
*p*TSOH	*para*-Toluenesulfonic acid
rt	Room temperature
TBAF	Tetrabutylammoniumfluoride
TBDMS	*tert*-Butyldimethylsilane
TBDPS	*tert*-Butyldiphenylsilane
TBOx	Tethered bis(8-quinolinato)
TES	Triethylsilyl
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
Tol	Toluene

Chapter 1

Introduction : Allylation of Carbonyl Compounds

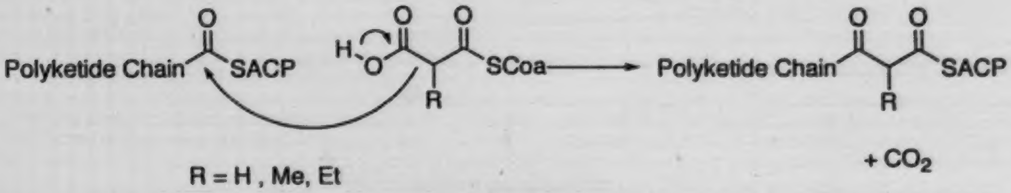
1.1 Allylation of carbonyl compounds

Over the past 40 years, enantioselective reactions have been the main driving force in organic synthesis. Many of these reactions have been discovered while investigating chemical problems posed by Nature itself. Among these methods, the allylation of carbonyl compounds (Equation **1-1**) has stood out as an extremely useful tool.[1] The success of this reaction is mainly due to the fact that when allylmetal species react with aldehydes, two new contiguous stereogenic centers are potentially generated. In some cases, these two centers can be obtained with outstanding stereocontrol. This type of carbon unit is closely related to propionate or acetate units found in a very important class of natural products, the polyketides.



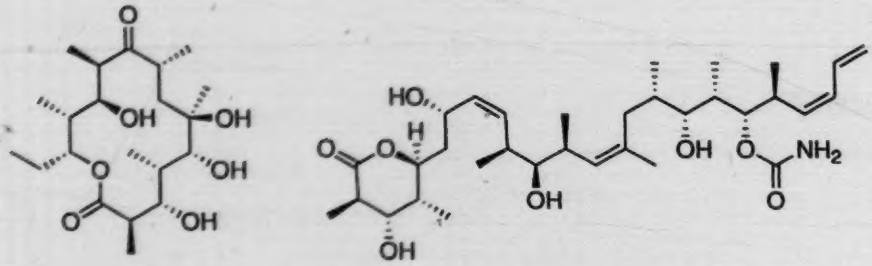
Equation 1-1

As long as organic chemistry has been around, Nature has provided organic chemists with an unlimited supply of interesting and biologically relevant molecules. In recent years, polyketides have attracted a lot of attention mainly because of their wide range of interesting biological properties such as anticancer, antibacterial, antifungal and more. The polyketides include a large number of molecules isolated from a wide range of organisms, terrestrial as well as marine ones. Polyketide natural products have the common feature that they arise from the condensation of acetate or propionate units. Biosynthetically, these units arise from condensation of polyketideCoA and either malonylCoA in the case of acetate units or methylmalonylCoA in the case of propionate units as it is simply described in Equation **1-2**. The process is mediated by an enzyme called polyketide synthase that controls and repeats the reaction until the final chain is assembled.[2]



Equation 1-2

Since Corey's first synthesis of erythronolide B[3] in 1978 (Figure **1-1**), the number of total syntheses of molecules of that family has been growing every week.

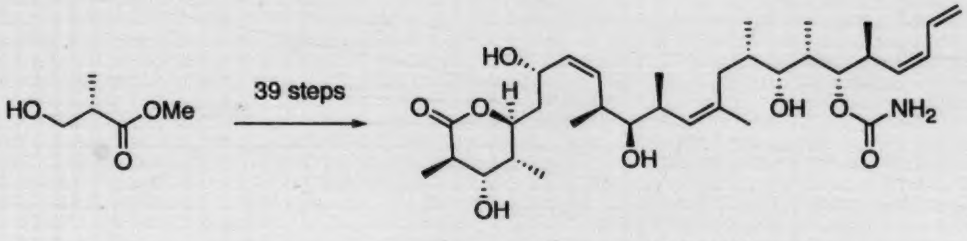


erythronolide B

(+)-discodermolide

Figure 1-1 Structure of Polyketides

The importance of this class of molecules is highlighted in the 2004 disclosure by chemists at Novartis of the synthesis of 60 grams of the antitumor agent (+)-discodermolide[4] (Figure **1-1**) for phase I clinical trials (Equation **1-3**). Although this large-scale synthesis does not make use of allylboration chemistry, it is a testament to the potential of polyketides for drug therapy. Their synthesis required 39 steps including 17 chromatographic purifications.

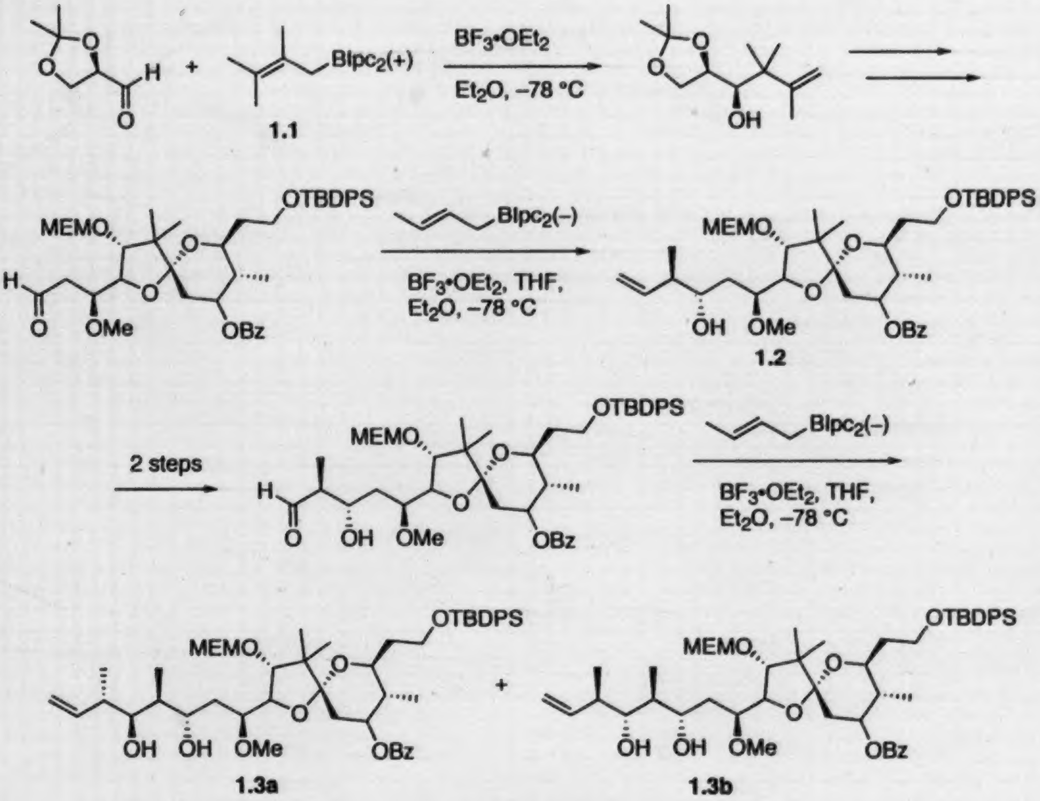


60 grams (+)-discodermolide

Equation 1-3

Since allylboration provides an exceptionally selective and operationally simple way of accessing acetate or propionate units, this makes polyketides prime targets for synthetic endeavors using this reaction. Many groups have used this approach in the past to synthesize molecules of that family. A few selected examples of allylboration reaction in natural product synthesis are presented in Schemes **1-1** to **1-3**.

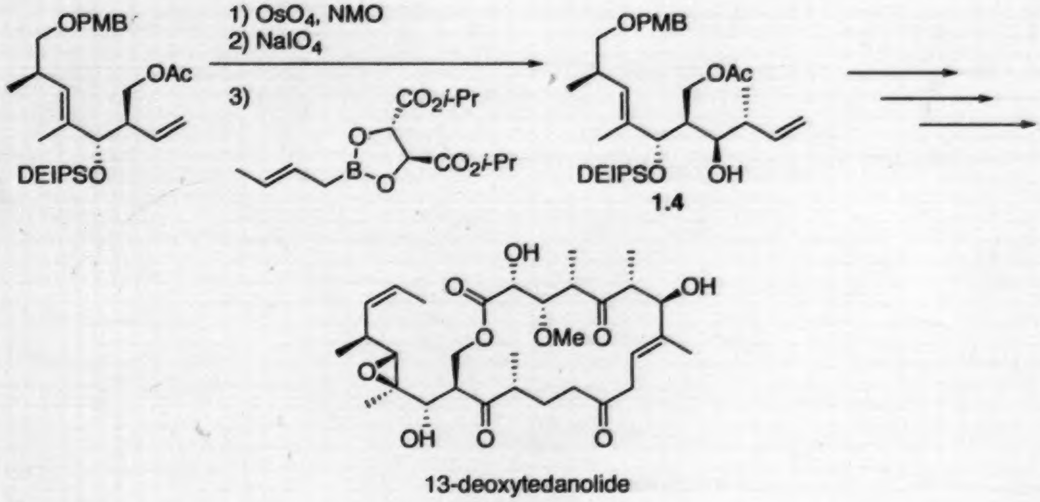
The first example is a synthesis by Armstrong and co-workers.[5] In the course of their synthesis of calyculin C (Scheme **1-1**), multiple allylboration reactions were employed. In the first case, they used a tri-substituted reagent **1.1** that provided the desired intermediate in 73% yield with excellent stereoselectivity. The second allylboration reaction was performed using the *E*-crotyldiisopinocampheyl reagent to afford the desired key fragment **1.2** in 55% yield with excellent diastereomeric control (>99:1 d.r.). This synthesis also shows the limitation of this type of methodology where in the third application, using the same *E*-crotyl reagent, the advanced intermediate **1.3** was formed without any selectivity, giving a one to one mixture of the two possible diastereoisomers.



BIpc$_2$(+)
1.1
BF$_3$•OEt$_2$
Et$_2$O, −78 °C
OH
OTBDPS
MEMO
H
O
OMe
OBz
BIpc$_2$(−)
BF$_3$•OEt$_2$, THF, Et$_2$O, −78 °C
1.2
2 steps
1.3a
1.3b

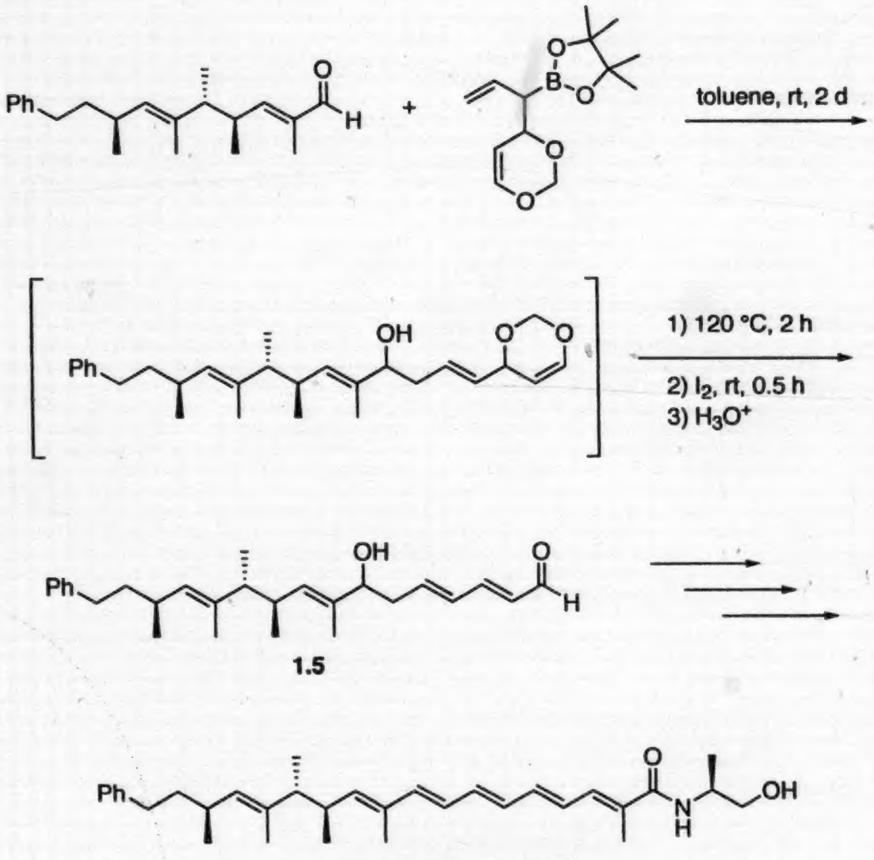
Scheme 1-1

In the next example, the group of Smith[6] synthesized 13-deoxytedanolide using Roush's *E*-crotyl boronate reagent derived from (*S,S*)-diisopropyl tartrate to prepare intermediate **1.4** (Scheme **1-2**). This key fragment was obtained in 63% yield with excellent diastereoselectivity, providing the desired product as a single diastereoisomer. In this case, the oxidative work-up required for Brown's allylation method proved to be too harsh for the aldehyde substrate. The milder Roush conditions proved to be more suitable while still providing the required diastereocontrol.


OPMB
OAc
DEIPSO
1) OsO4, NMO
2) NaIO4
3)
CO2i-Pr
CO2i-Pr
OPMB
OAc
DEIPSO
OH
1.4
OH
OH
OMe
O
O
O
OH
O
O
13-deoxytedanolide

Scheme 1-2

At first glance, phenalamide A_2 (**1.6** in Scheme **1-3**) does not look like a suitable target for the application of the allylboration reaction. Nonetheless, in Hoffmann's synthesis of phenalamide A_2,[7] an α-substituted allylboronate was used to introduce the triene unit in the desired intermediate **1.5** with excellent yield (69%). The obtained intermediate was then succinctly transformed into the desired natural product. This example showcases the potential of such α-substituted allylboronates that contain chemically useful and relevant functional groups.


Ph
O
H
+
O
B
O
O
O
toluene, rt, 2 d
Ph
OH
O
O
1) 120 °C, 2 h
2) I2, rt, 0.5 h
3) H3O+
Ph
OH
O
H
Ph
O
N
H
OH

1.5

phenalamide A_2 (**1.6**)

Scheme 1-3

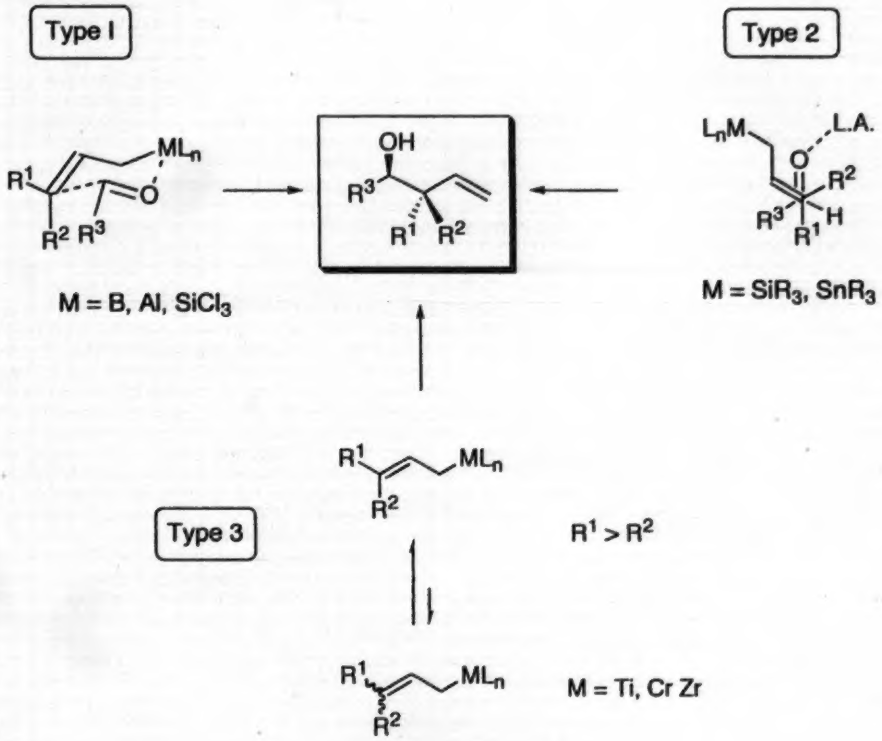
This short list of examples illustrates the potential of the allylboration reaction in applications to natural product synthesis. These syntheses also demonstrate some of the remaining limitations of the allylboration reaction.

1.2 Types of allylmetal species

In 1983, Denmark classified allylation reagents into three types.[8] Type 1 is referring to reagents where the relative stereochemistry of the product is reflective of the geometry of the starting allylmetal species. The Type 1 reagents include boron, aluminum, and electron deficient trichlorosilanes. The high level of stereochemical transfer is due to the nature of their transition states. The reaction of reagents of Type 1 proceeds through a closed chairlike transition state (Scheme **1-4**).

The Type 2 reagents are typically those containing trialkyl tin and trialkyl silicon, excluding the above-mentioned trichlorosilanes. These reagents are said to be stereoconvergent: they produce the *syn* product predominantly regardless of the geometry of the starting material. This is the result of an open chain transition state (Scheme **1-4**).

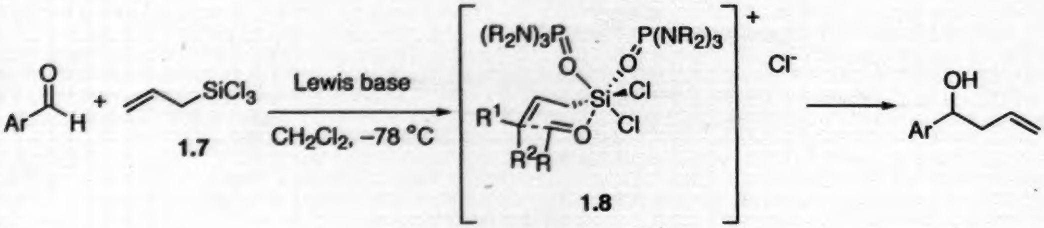
The last type of reagents, Type 3, refers to reagents that first go through an isomerization of the double bond leading to the most stable (*E*)-allylmetal reagent (Scheme **1-4**). Due to this isomerization, this process is also stereoconvergent leading to the *anti* product predominantly. This is the case of allylmetal species containing titanium, chromium or zirconium. In most cases, after equilibration, the reaction proceeds through a closed chairlike transition state similar to that of Type 1 reagents.


Type I
Type 2
Type 3
ML$_n$
R^1
R^2
R^3
O
M = B, Al, SiCl$_3$
OH
L$_n$M
L.A.
H
M = SiR$_3$, SnR$_3$
R^1 > R^2
M = Ti, Cr Zr

Scheme 1-4

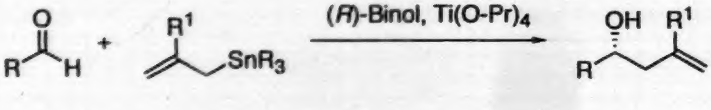
1.3 Catalytic enantioselective allylation

In recent years, catalytic enantioselective methods to achieve the allylation of carbonyl substrates have been developed. These methods include Denmark's allyltrichlorosilanes[9] and Keck's allylation.[10] In the case of Denmark's allylation (Scheme **1-5**), the electron deficient trichlorosilane **1.7** interacts with the carbonyl substrate to form a closed transition state of the Type 1 reagents. This pentacoordinate silicon species is then activated by two molecules of the Lewis base to form a hexacoordinate siliconate species **1.8**. By using chiral bisphosphoramides, excellent enantioselectivity can be achieved with aromatic aldehydes. Unfortunately, this reaction fails with aliphatic aldehydes.


Ar
H
O
+
SiCl3
1.7
Lewis base
CH2Cl2, −78 °C
(R2N)3P
P(NR2)3
O
Si
Cl
R1
R2
R
1.8
+
Cl-
OH
Ar

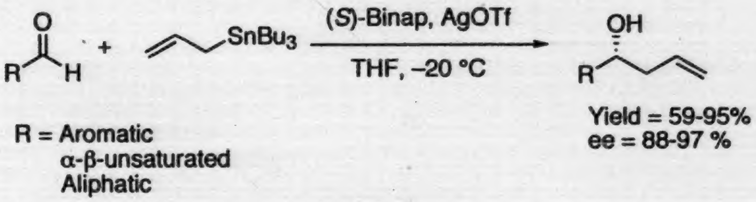
Scheme 1-5

In the case of the Keck allylation (Equation **1-4**), the reaction proceeds through the Type 2 open transition state where the titanium(IV) binol complex serves as a chiral Lewis acid and activates the aldehyde. Since the reaction occurs through the Type 2 transition state, this system cannot be use for applications in diastereoselective crotylations.


O
R
H
+
R1
SnR3
(R)-Binol, Ti(O-Pr)4
OH
R1
R

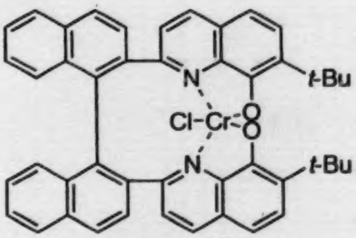
Equation 1-4

Other pioneering work in enantioselective catalytic allylation includes work by Yamamoto on the silver catalyzed allylstanation of aldehydes (Equation **1-5**).[11] This catalytic manifold generates acceptable to excellent yield (59-95%) and good to excellent enantioselectivity (88-97%). This method is particularly successful with aromatic aldehydes, in which cases the best enantioselectivities are obtained. The lower selectivity results are from the addition onto α-β-unsaturated and aliphatic aldehydes. One major limitation of this method is the need for one equivalent of allyltributyltin species, which renders it environmentally unfriendly.



Equation 1-5

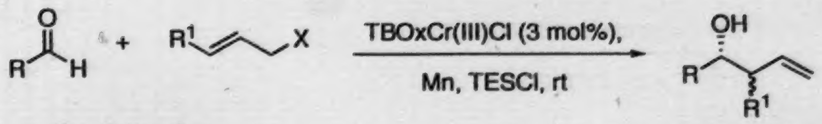
Just recently, Xia and Yamamoto reported the use of a tethered bis(8-quinolinato) (TBOx) chromium complex (Figure **1-2**) as catalyst for aldehyde allylation using allylic halides (Br and Cl) (Equation **1-6**).[12]



TBOxCr(III)Cl

Figure 1-2 Structure of TBOxCr(III)Cl Catalyst

In this method, the catalyst reacts first with the allylic halide to form the allylic chromium species, which then proceeds to do the typical Type I allylation reaction. In the case of the simple allylation reaction, excellent yield (75-95%) and excellent selectivity (86-98%) are obtained with a wide range of aldehydes (aromatic, α-β-unsaturated, and aliphatic). This catalytic manifold was extended to the case on γ-substituted allyl reagents. Although in this case, the yield and enantioselectivity are still excellent, the diastereoselectivity is low, varying from 4.2:1 to 10.3:1. This ratio variation can be correlated with the steric bulk from both the aldehyde side chain and the R^1 group; the bigger these groups get the higher the ratio obtained.



R = Aromatic
α-β-unsaturated
Aliphatic
R^1 = H, Me or alkyl
X = Br, Cl

Yield = 54-95%
ee = 86-97 %
d.r. = 4.2:1-10.3:1

Equation 1-6

Due to the fact that boron reagents are of the Type 1, and because boron acts as an internal Lewis acid that activates the aldehyde, no attempts to catalyze the allylboration reaction were made until recently.

1.4 Allylboration of carbonyl compounds

Amongst all carbonyl allylation methods, the allylboration reaction stands out due to a number of features. Since they are Type 1 reagents, allylic boron compounds demonstrate a high level of predictable stereoselectivity in the generation of homoallylic alcohols. Other features worth mentioning are: the low toxicity of boron, and the relative generality of the reaction. Mikhailov and Bubnov reported the first allylboration reaction in 1964.[13] It was observed at that time that allylboron species could transfer allyl groups onto carbonyl groups. One of the major breakthroughs for this reaction was the report in 1979 by Hoffmann and co-workers[14] of the exceptional diastereospecificity of the reaction when the allyl group is γ-substituted. This discovery was then followed by the development of stoichiometric enantioselective versions of this reaction, with significant contributions by the groups of Hoffmann,[15] Brown,[16] Roush,[17] Masamune,[18] and Corey[19] in the 1980's. Until the recent work of Chong[20] and Soderquist,[21] few enantioselective allylation methods were successfully extended to ketone allylation.

1.4.1 Types of allylboration reagents

Boron allylating reagents can be separated in three groups (Figure **1-3**). Trialkyl boranes are reagents where boron is attached to three carbon atoms, and boronates are those in which the boron atom is attached to one carbon and two alkoxy groups. Trifluoroborate salts are anionic boron species that contain one carbon-boron bond and three fluorine substituents.

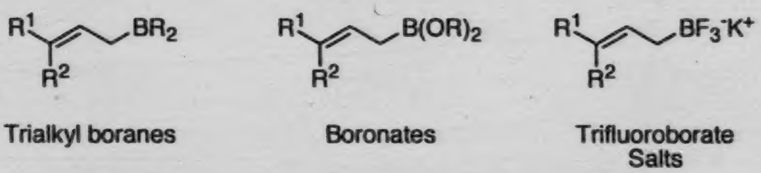
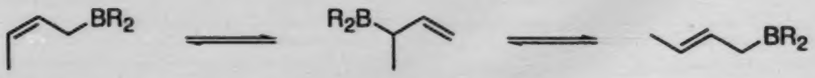


Figure 1-3 Type of Allylic Boron Reagents

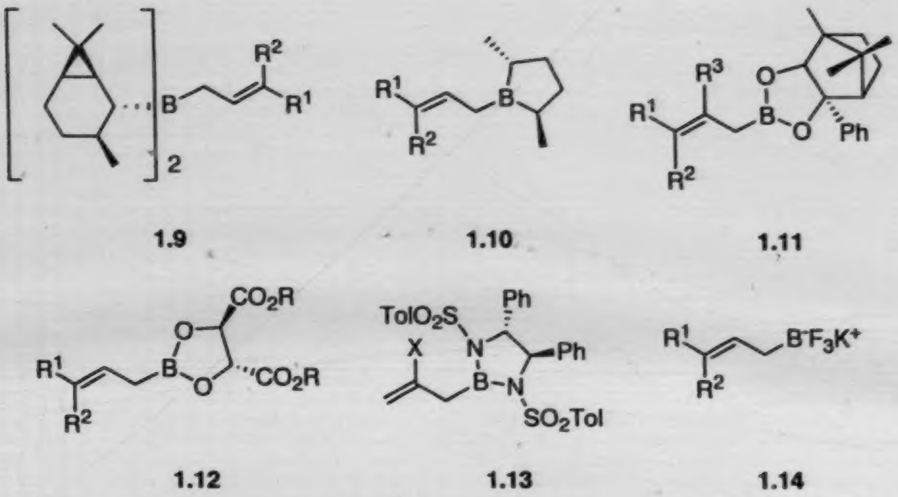
The main characteristics of dialkyl allylic boranes, such as the Brown diisocaranyl or diisopinocampheyl boranes (**1.9** in Figure **1-4**), are as follows:

they are very reactive (reactions are typically carried at –78 °C and completed within a few hours), and they are also air and moisture sensitive, making them hard to handle. Despite these limitations, Brown's reagents are the current benchmark in terms of selectivity for the simple allylation reaction, affording the products with ee's >94%.[16] When performed with removal of the magnesium salts formed in their preparation, and run at –100 °C, the enantioselectivity rises up to 99%.[22] In the case of the *E* and *Z* crotyl reagents, the enantioselectivity is significantly reduced to 88-90%. This lower level of selectivity renders these reagents significantly less appealing for the crotyllation reactions. These γ-substituted reagents also suffer from a conformational instability; the *cis* reagents readily isomerize to the more stable *trans* reagents through a 1,3-borotropic shift (Scheme **1-6**). This rearrangement is very rapid at temperatures above –45 °C and leads to a complex mixture of products.[23]



Scheme 1-6

In the case of Masamune's system (**1.10** in Figure **1-4**), the level of enantioselectivity is almost perfect,[18] but preparing the reagent requires four synthetic operations including two resolution steps.[24]



1.9 1.10 1.11

1.12 1.13 1.14

Figure 1-4 Structure of Allylic Boron Species

On the other hand, allylboronates derived from chiral diols such as Hoffmann's camphor-derived diol and Roush's tartrate esters are much more stable and can be easily stored at room temperature. Most can be purified by distillation or even in some cases by flash chromatography. These reagents have a significantly improved stability in the case of the γ-substituted reagents. Indeed, the 1,3-borotropic shift occurs at much higher temperatures and is seldom observed in the course of carbonyl additions. Unfortunately, they suffer from a lack of reactivity that calls for running the reaction at higher temperature at the expense of enantioselectivity. In the case of Hoffmann's reagents (**1.11** in Figure **1-4**),[14,25,26] the reaction is typically run at a temperature of –40 °C and provides ee's in the range of 24-86%. In the case of the tartrate-based reagents (**1.12** in Figure **1-4**),[17] although the reaction is rapid at –78 °C, it requires the presence of molecular sieves and can only provide ee's in the range of 75-85%. The addition of tartrate-derived allylboronates is very successful with α-chiral aldehydes giving excellent double diastereoselectivity.

The bis(sulfonamide) reagent developed by Corey[19] (**1.13** in Figure **1-4**) is generated *in situ* from the corresponding allylstannane. This feature is the source of most of the limitations for this method. The presence of an equimolar amount of tin in the reaction prevents the common use of the reagent due to the health and environmental concerns caused by alkyltin residues.

The allylic trifluroborate salts[27] (**1.14** in Figure **1-4**) benefit from extended shelf life stability. This improved stability allows them to be easily purified by crystallization. These reagents are easy to handle and do not require any special attention besides the need to use plastic containers for storage due to the reactivity of common glass towards fluorine. By their nature, allylic trifluoroborate salts are anionic reagents and they require the presence of $BF_3{\cdot}OEt_2$ to become reactive. This Lewis acid removes a fluoride anion from the boron atom in order to liberate the p-orbital of boron. This empty orbital can now activate the carbonyl compound to be allylated and allows for the formation of the reactive six-membered ring transition state. In the case where an excess of $BF_3{\cdot}OEt_2$ is used, these additions are particularly efficient and are complete in 15 minutes at –78 °C. If a catalytic amount of the Lewis acid is used, typically 5 mol %, the reaction is complete within 3-6 h at room temperature. The presence of the fluoride on the boron makes it difficult to envisage an enantioselective variant of the trifluoroborate salt additions. Allylic trifluoroborate salts maintain the high level of diastereoselectivity associated with other classes of boron allylating reagents.

Many of the above classes of reagents have been extended to various types of substituted allyl group transfer (Figure **1-5**). The simplest group is the unsubstituted allyl group containing only the necessary three carbons. Substitution can easily be tolerated at the α-position, at the β-position (if R^1 = Me, methallyl), and at the γ-position (if R^1 = Me and *cis*, *Z*-crotylation, if R^1 = Me and *trans*, *E*-crotylation). It is also possible to use the allylboration reaction to introduce other unsaturated functionalities such as allenyl and propargyl groups.

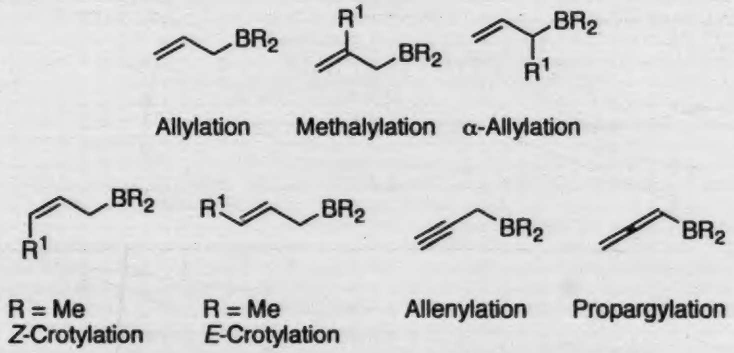
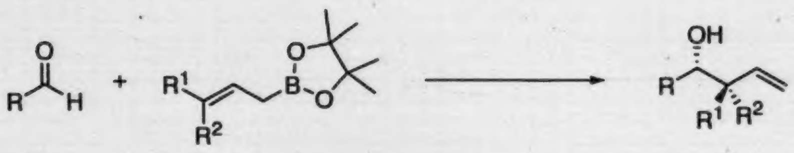

BR2
Allylation
R1
BR2
Methalylation
BR2
R1
α-Allylation
BR2
R1
R = Me
Z-Crotylation
R1
BR2
R = Me
E-Crotylation
BR2
Allenylation
BR2
Propargylation

Figure 1-5 Structure of Transferable Groups

1.4.1.1 Mechanism of the carbonyl allylation reaction

The mechanism of the allylboration remained uncertain for almost 20 years after its discovery. The observation made by Hoffmann and co-workers[14] in 1979 that the allylboration reaction was stereospecific was one of the first pieces of the puzzle. A *Z*-substituted allyl species generated specifically the *cis* allylboration product as well as the *E*-substituted reagent would generate the *trans* product (Equation 1-7).



Equation 1-7

This provided stong evidence for the proposed six-membered ring transition state structure. Li and Houk[28] studied by *ab initio* molecular orbital calculations the addition of allylboronic acid on formaldehyde. Their calculations predicted that the transition state of the reaction should be in a closed six-membered ring and be significantly more stable in the chair conformation.

To gain further knowledge about the allylboration reaction, Brown has studied the effect of the nature of the boron species on the rate of the reaction.[29]

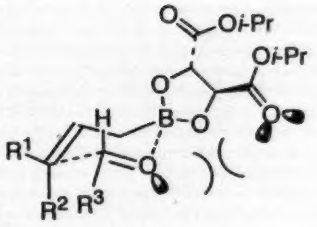
From these observations, Brown has concluded that the more electron poor the boron atom, the faster the reaction occurs. The following factors will influence the electronic density at the boron center. First, the nature of the three groups on boron has the major influence, even if, in appearance, electronegativity should be the dominating factor. In fact, the most important factor is the ability of the adjacent atom to undergo back-bonding with the empty p orbital of boron. The stronger this back-bonding is, the less reactive the reagent will be, leading to slower reactions. This effect explains the following order of reactivity: boranes > azaborolidines > oxoboronates. The second important factor, in the case of cyclic boronates, is the ring size, which has a major impact since it influences the back-bonding ability of the oxygen atom. The reactivity of six-membered boronates is significantly lowered compared to those with five-membered rings. This is due to the significantly better overlap of the lone pair from oxygen with the empty p-orbital of boron in the case of the six-membered ring boronates.

Another factor explaining the increased reactivity of the five-membered boronates is due to the complexation of the carbonyl's oxygen with the boron atom. At that point, the boron atom rehybridizes and goes from sp^2 to sp^3. When boron attains the tetrahedral geometry, it releases the steric strain of having an sp^2 atom in the ring, the "ring strain release" effect. This effect is less pronounced in the case of the six-membered ring, which better accommodates the sp^2 boron atom. In addition, steric factors can also be involved in the relative rate of the allylboration reaction. For example, pinacol allylboronates are at least three times less reactive than the allylboronates derived from ethylene glycol.

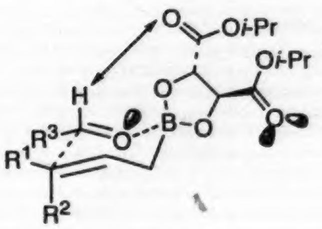
The experimental observations of Brown and co-workers[29] were confirmed with calculations performed by the group of Omoto.[30] Their calculations using the *ab initio* MO method found that, at the transition state, there is very little C-C bond character and a very strong B-O interaction. This is a good reflection of the increased reactivity of electron deficient boronate species (i.e., more Lewis acidic) since it favors a stronger B-O interaction.

1.4.1.2 Source of stereochemical induction in the carbonyl allylation reaction

Since the development of the enantioselective allylboration reaction, a lot of effort has been devoted into explaining what factors influence the observed selectivities. For the Roush system, it was proposed that two factors may have an impact on the stereochemical outcome of the reaction (Figure **1-6**).[31] First, electrostatic repulsion between the oxygen lone pairs of the aldehyde and the tartrate ester carbonyl oxygen (**A**, Figure **1-6**) should disfavor the approach of the aldehyde from the same side. This interaction is minimized in transition state **B** (Figure **1-6**). Secondly, it was also proposed that a favorable n-π^* interaction between the lone pair of the ester carbonyl oxygen with the π^* orbital of the aldehyde carbonyl is involved in the transition state. This interaction is only possible in transition state **B**. Since both of these factors are favoring transition state **B**, they are generally accepted as the origin of stereoinduction for this class of allylboron reagents. In the case of Hoffmann's camphor-derived diol,[25] it was proposed that a π–π^* interaction between the π system of the aromatic and the π^* orbital of the aldehyde, as depicted by **1.15** in Figure **1-6**, is the factor determining the enantiofacial selectivity. In the cases of Brown's, Masamune's and Corey's systems, minimization of steric interactions is the source of selectivity in these reactions. In the Brown system (**1.16** in Figure **1-6**), minimization of the interaction between the chiral isopinocampheyl (Ipc) methyl groups and the methylene group of the transferable allyl group is thought to direct the approach of the aldehyde. For Masamune's system (**1.17** in Figure **1-6**), the interaction between the methyl group α to the boron and the methylene group of the transferable allyl group should direct the approach of the aldehyde from the same face.

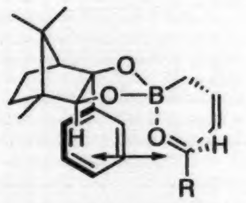

O
Oi-Pr
Oi-Pr
O
B-O
H
R1
O
R2 R3

A

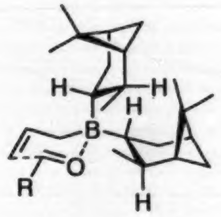

O
Oi-Pr
Oi-Pr
H
R3
R1
O
B-O
O
R2

B

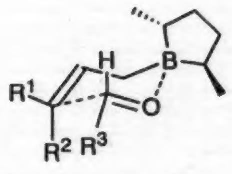
Roush



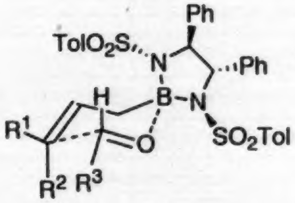
1.15



1.16



1.17

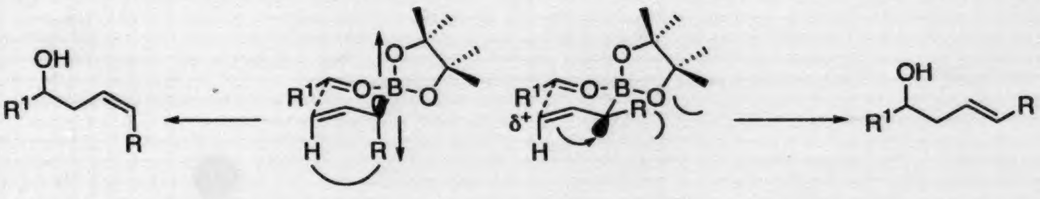

Ph
TolO2S
N
Ph
H
B-N
R1
O
SO2Tol
R2 R3

1.18

Figure 1-6 Induction of Enantioselectivities

In Corey's system (**1.18** in Figure **1-6**), the interaction between the toluene sulfonamide groups and the methylene group of the allyl transferable group is minimized in the transition state, which determines the enantioselectivity of the reaction.

Another approach towards enantioselective allylboration is the use of chiral α-substituted reagents. These reagents are known to provide good to excellent transfer of chirality. In this case, the main challenge is their preparation, which, to this day, is still a major limitation. In the few cases where it is possible to generate them in an enantioselective fashion,[32,33] these reagents have proved to be very useful. The selectivity of the reaction is influenced by three factors. The first factor is the steric interaction created by the presence of the α-R group. This group interacts with the group on the boron (**1.20** in Figure **1-7**). It is also interacting with the group at the γ-position (A1,3 allylic strain). This steric interaction arises between this α-R group and the group *cis* to the boronate in the allyl moiety (**1.19** in Figure **1-7**). In the case of a large boron substituent, the interaction with the boronate group is typically the dominant factor. The second factor is of electronic nature. When the R group is polar, like halides or methoxy groups, this axial arrangement is even more favorable due to minimization of the dipole moment between the C-R bond and the axial B-O bond (**1.19** in Figure **1-7**). The last factor, also of electronic nature, is the presence of orbital overlap between the π-system of the allyl group and the σ^* of the C-R bond, as shown by **1.19** in Figure **1-7** where this interaction is minimized. The orbital overlap shown in **1.20** (Figure **1-7**), will create an electron deficiency at the γ-position of the allyl. In consequence, this will slow down the reaction since this γ-position needs to attack in a nucleophilic fashion onto the aldehyde carbonyl's.



1.19 **1.20**

Figure 1-7 Transition State for the Addition of α-Substituted Allylboronates

1.4.1.3 Double diastereoselectivity

The allylboration reaction, through its tightly closed chairlike transition state, provides a high level of stereoselectivity. In general, enantioselectivity can be controlled by the nature of the allylboration reagent. However, in the case where the allylation is performed onto an α-chiral aldehyde, the control of the stereochemical outcome can be altered.[34,35] In this case, *syn*-pentane interactions can become the main factor influencing stereochemistry. When looking at the addition of *E*-crotyl (***E*-1.21**, R^1 = Me) and *Z*-crotyl (***Z*-1.21**, R^2 = Me) reagents to the *S*-aldehyde **1.22**, four transition states with the H group inside the chair are possible (Figure **1-8**). In the case of the *E*-crotyl reagent (***E*-1.21**, R^1 = Me, R^2 = H), transition state **1.26** is the most favorable. In this case, the H group of the aldehyde is aligned with the methyl of the crotyl reagent, while at the same time, the second smallest group of the chiral aldehyde, the methyl group in this case, is aligned with the H group of the crotyl reagent. The minimization of the two main *syn*-pentane interactions leads to the *anti* Felkin product. In the case of transition state **1.23**, the *syn*-pentane interaction between the large ethyl group of the chiral aldehyde and the H group of the crotyl reagent renders this transition state less favorable. The alignment of the two methyl groups in transition state **1.24** creates a significant unfavorable *syn*-pentane interaction. In transition state **1.25**, a similar interaction is generated between the large ethyl group of the chiral aldehyde and the methyl group of the crotyl reagent, thus significantly disfavoring this transition state.

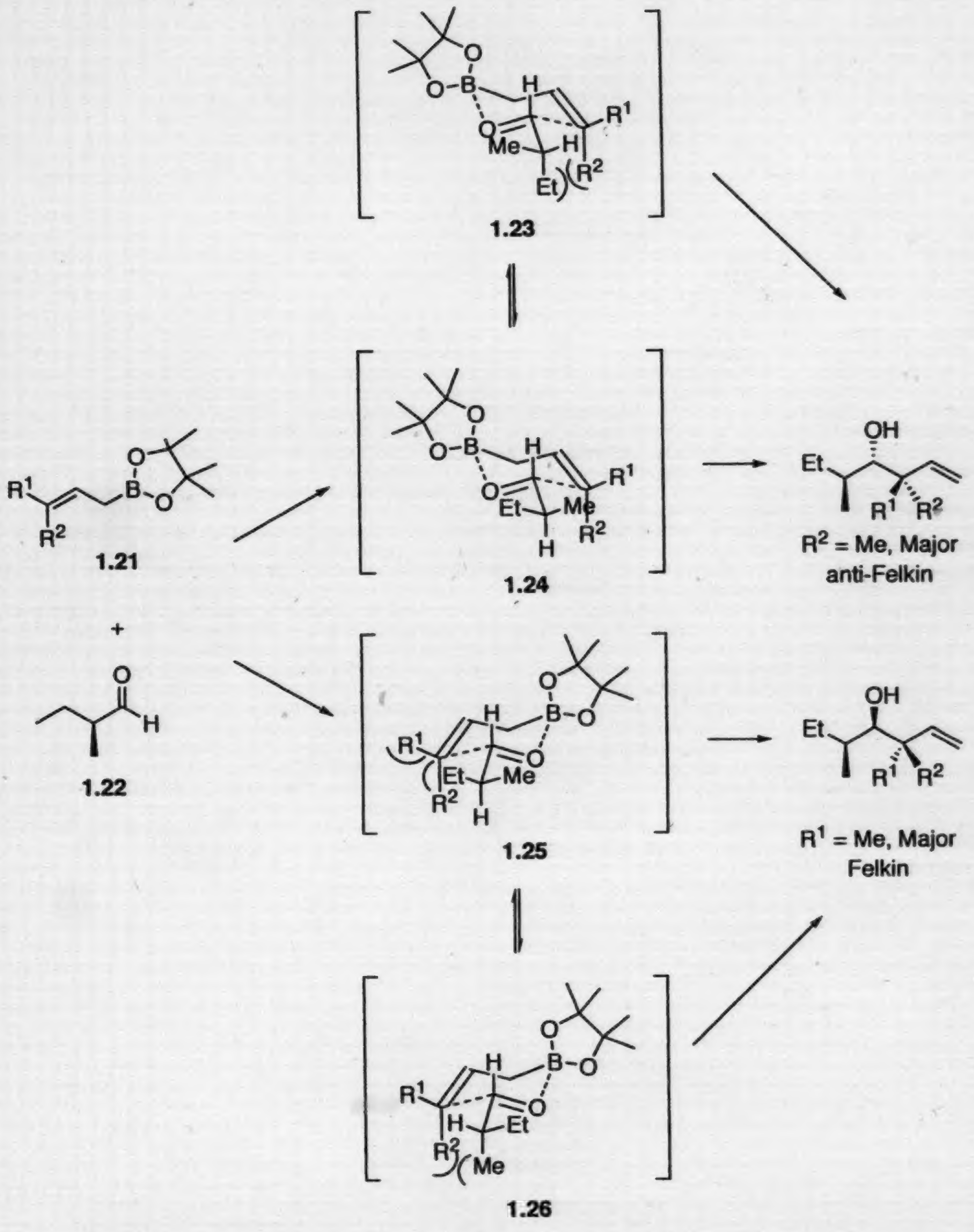
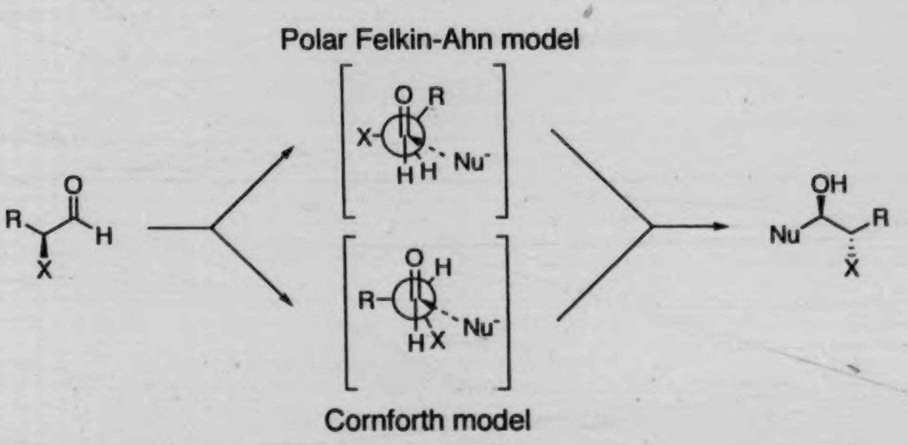

1.21
+
1.22
1.23
1.24
1.25
1.26
R¹
R²
Et
Me
H
OH
R² = Me, Major
anti-Felkin
R¹ = Me, Major
Felkin

Figure 1-8 Transition State of the Crotyl Addition to α-Chiral Aldehydes

For *Z*-crotyl reagents (R^1 = H, R^2 = Me), the same *syn*-pentane interactions are directing the course of the reaction (Figure **1-9**). In this case, the most favorable transition state is **1.24** where the *syn*-pentane interactions are minimized. Precisely, the H group of the aldehyde is aligned with the methyl of the crotyl reagent, while the small methyl group of the chiral aldehyde is aligned with the H of the crotyl reagent. This combination of steric interactions gives rise to the *syn* (anti-Felkin) product as the major product. In transition state **1.23**, a major *syn*-pentane interaction arises between the large ethyl group of the aldehyde and the methyl group of the *Z*-crotyl reagent. Transition states **1.25** and **1.26** suffer from similar interactions. The *syn*-pentane relationship between the ethyl of the aldehyde and the H of the crotyl, and between the methyl of the aldehyde and the methyl of the *Z*-crotyl reagent, respectively, are responsible for the exclusion of these two pathways.

In the case of α-chiral aldehydes bearing a polar substituent, like alkoxy and amino groups, the inductive effect can overrule the steric bias of the aldehyde. To explain the outcome of allylborations of this type of aldehydes, two models can be invoked: the polar Felkin-Ahn model and the dipole minimization model proposed by Cornforth (Equation **1-8**).[36]



Equation 1-8 Model of Nucleophilic Addition on Polar α-Substituted Aldehydes

In this case, either of the two models predicts that the same 1,2-*anti* product will be formed. In the case of the simple allylation reaction, the four transition states not having the H group of the α-chiral aldehyde outside the chair are the most reasonable ones. Of these, transition state **1.32** corresponds to the polar Felkin-Ahn model, and transition state **1.31**, where the X group is *anti* to the carbonyl, corresponds to the Cornforth model (Figure **1-9**). The transition states **1.29** and **1.30** are rotamers of the polar Felkin-Ahn and Cornforth models respectively. Both of these transition states would result in the *syn* product, which is not the major product observed in this reaction.

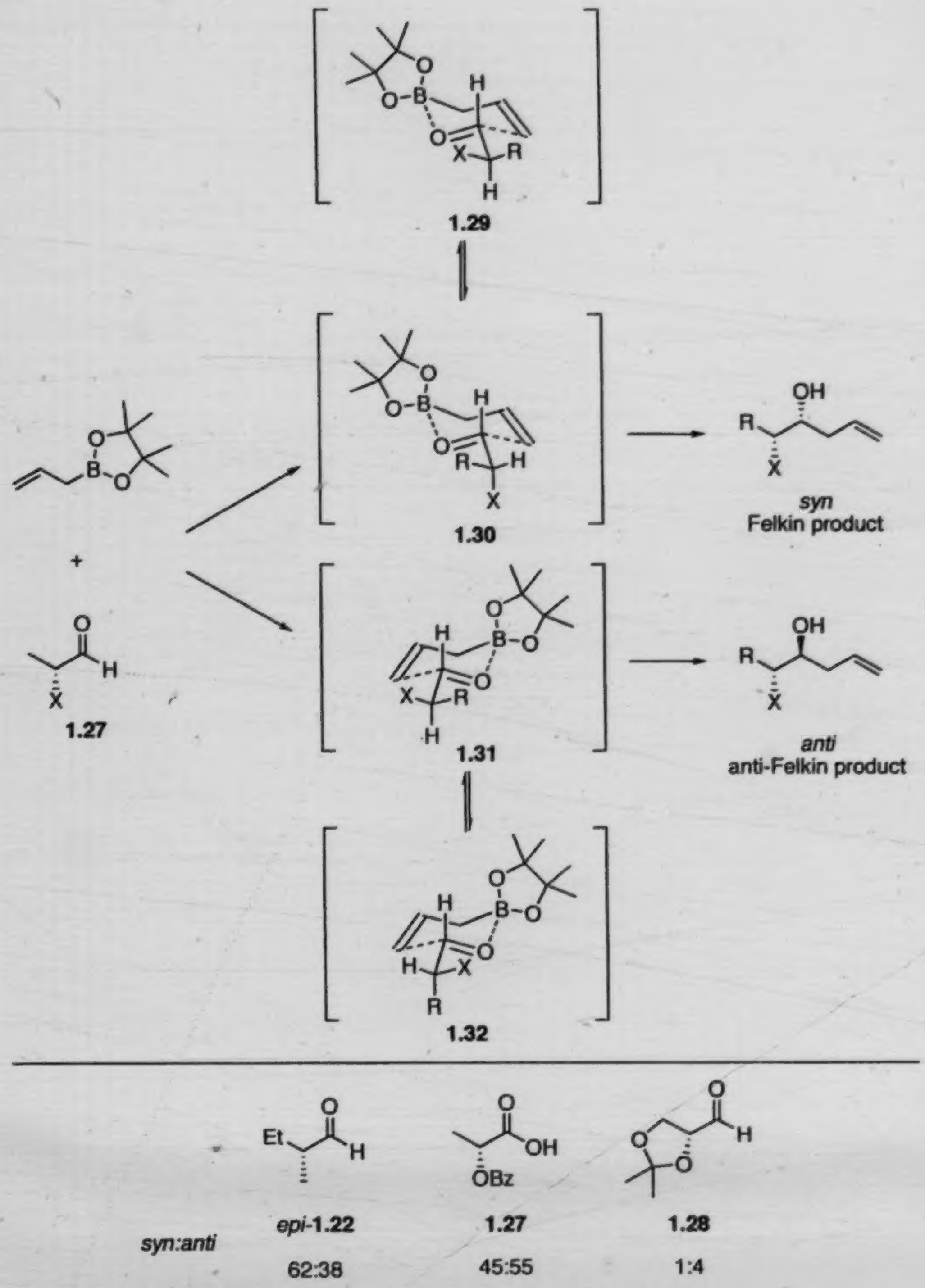
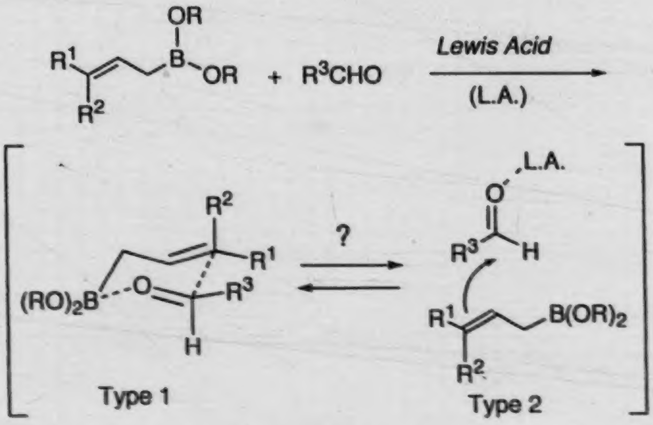

1.29
1.30
1.31
1.32
1.27
syn
Felkin product
anti
anti-Felkin product
syn:anti
epi-1.22
62:38
1.27
45:55
1.28
1:4

Figure 1-9 Transition State for the Allylation of polar α-Substituted Aldehydes

It is interesting to note that upon reaction with α-chiral aldehydes that do not possess a polar group, such as aldehyde *epi*-**1.22**, the reaction provides a mixture of ~2:1 in favor of the *syn* product. The introduction of a benzyloxy group reverts the selectivity to 55:45 slightly in favor of the *anti* product **1.27**. When glyceraldehyde derived aldehyde **1.28** is used, this time a ratio of diastereoisomers of 4:1 in favor of the *anti* product is obtained. This series of examples is an excellent representation of the effect of an α-polar substituent on the aldehyde substrate in the allylboration reaction.

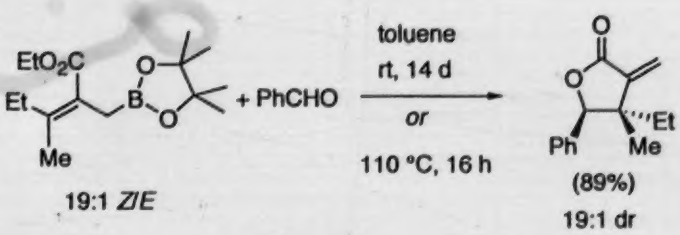
1.4.2 Lewis acid-catalyzed allylboration

Even if allylboronate reagents are significantly easier to prepare, purify, and manipulate than allylborane reagents, their synthetic usefulness is limited due to their relative lack of reactivity or low selectivity. If we take into account that this is due to the electron donating ability of the oxygen atoms adjacent to the boron atom, one could reasonably assume that if this back-donation phenomenon were reduced, a corresponding increase in reactivity should be observed. The Roush tartrate boronate system backs this assumption since the presence of the electron withdrawing carboxyesters makes it significantly more reactive than other boronates for the allylboration reaction. Unfortunately, an increase in reactivity often occurs to the detriment of selectivity. In general, the catalytic approach can be used to increase the reactivity of poorly reactive reagents. In the case of allylboration, Lewis base catalysis can be ruled out since the Lewis acidity of boron is required for the reaction to proceed. The prospect of Lewis acid catalysis raises major interrogation as to the type of transition state that would result with such an addition of an external Lewis acid. One can wonder if the reaction would still proceed through a closed chairlike transition state, or would rather go through a Type 2 open chain transition state, thus losing the diastereospecificity of the typical allylboration reaction as depicted in Equation **1-9**.

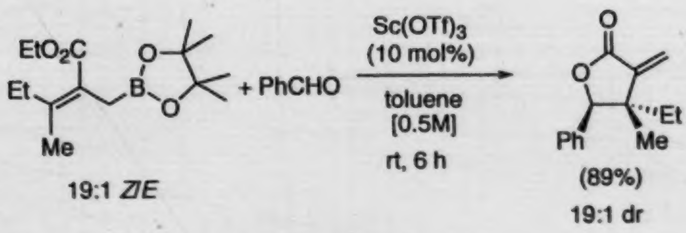


Equation 1-9

Fortunately, as it was demonstrated by Kennedy and Hall,[37,38] the diastereospecificity of the reaction is maintained and, in the particular case reported, the presence of the external Lewis acid gave rise to a significant increase of reactivity. Under catalysis, the allylboration reaction was completed in six hours at room temperature compared with over seven days at room temperature or sixteen hours at 110 °C without a catalyst (Equations **1-10** and **1-11**). In these studies, $Sc(OTf)_3$ and $Cu(OTf)_2$ stood out as particularly efficient catalysts.


EtO2C
Et
Me
19:1 Z/E
+ PhCHO
toluene
rt, 14 d
or
110 °C, 16 h
O
Ph
Et
Me
(89%)
19:1 dr

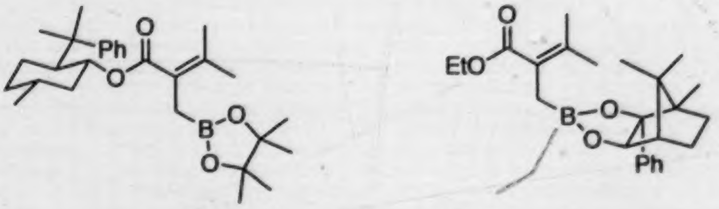
Equation 1-10


EtO2C
Et
Me
19:1 Z/E
+ PhCHO
Sc(OTf)3
(10 mol%)
toluene
[0.5M]
rt, 6 h
O
Ph
Et
Me
(89%)
19:1 dr

Equation 1-11

Based on these observations, Rauniyar and Hall undertook the challenge of studing the mechanism of this new catalytic manifold.[39] Their study presented numerous evidences indicating that boronate activation was the preferred mode of activation over aldehyde activation. One of the key experiments was the comparison of the increase in the reaction rate of the addition of allylborane to aldehyde with and without catalyst versus the increase in the reaction rate of the addition of allylboronate to aldehyde with and without catalyst. This experiment showed no acceleration in the addition of the allylborane and a 100 fold acceleration in the case of the boronate species. This was consistent with boronate activation since the aldehyde activation process would be expected to happen in both cases thus, accelerating the addition of allylborane as well.

Using $Sc(OTf)_3$ as catalyst, it was possible to render the reaction enantioselective by using a chiral auxiliary approach (Figure **1-10**).



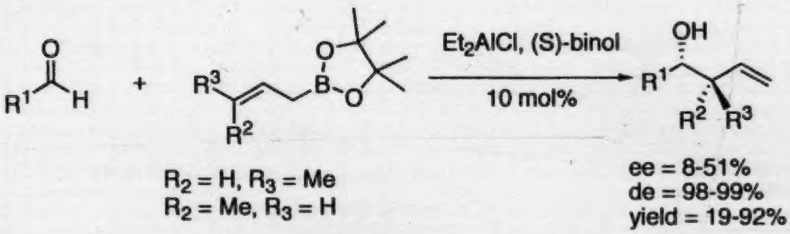
1.33 **1.34**

Figure 1-10 Structure of Chiral Allylboronates

A series of auxiliaries were investigated in this approach. On the ester group, (–)-8-phenylmenthanol (**1.33**) gave the best results and Hoffmann's (–)-camphor-derived diol was used as auxiliary on the boron (**1.34**). With this approach, the best result was obtained in the case of the (–)-8-phenylmenthanol auxiliary (**33**) using 10 mol % $Cu(OTf)_2$ in toluene. It afforded the desired product in 93% yield with 71% ee for the (*S*) enantiomer in the reaction of allylboronate **33** with decanal in just 24 hours at room temperature. This result compares well with the 80 % yield and 82 % ee obtained in the reaction with

TBDMSOCH$_2$CH$_2$CHO without catalyst at room temperature for fourteen days. Interestingly, under the same catalytic conditions, Sc(OTf)$_3$ provided the desired product in only 23% yield and 10% ee.

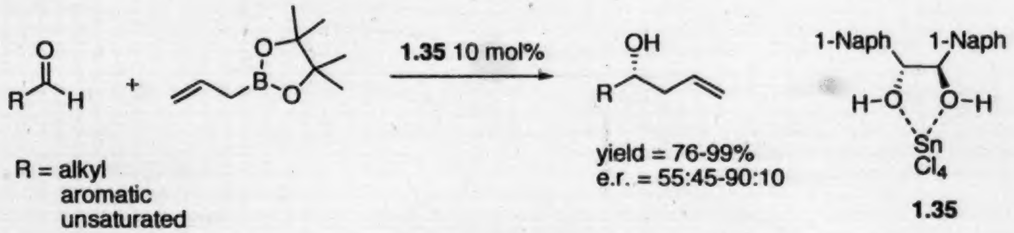
Shortly after the first report by Kennedy and Hall, the group of Miyaura[40] reported the first catalytic asymmetric allylboration reaction (Equation **1-12**).



Equation 1-12

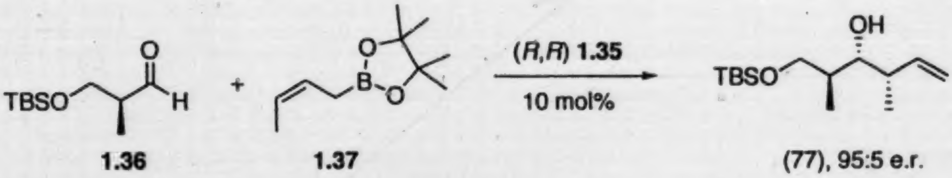
This report, despite its limited success, was the first example of a truly catalytic enantioselective allylboration. The best case reported is the example of a *E*-crotylation where the d.e. is 99% and the ee is 51%. In this report, no mechanistic proposal was given.

After completing their mechanistic studies, Rauniyar and Hall[41] developed a new approach towards enantioselective catalytic allylboration of aldehydes. The manifold that was successful for them was Brønsted acid activation of allylboronates. In the case of the simple allylation reaction using catalyst **1.35**, (Equation **1-13**) the catalytic condition achieved only limited success with generally excellent yields but with poor to moderate selectivities.


O
R
H
+
O
B
O
1.35 10 mol%
OH
R
R = alkyl
aromatic
unsaturated
yield = 76-99%
e.r. = 55:45-90:10
1-Naph
1-Naph
H-O
O-H
Sn
Cl4
1.35

Equation 1-13

Where this method became very interesting is in the case of double diastereoselection. In the case of the addition of *Z*-crotyl pinacol boronate (**1.37**) to α-chiral aldehyde **1.36** in the matched case, an enantiomeric ratio of 95:5 can be obtained (Equation **1-14**). This result is impressive considering the high level of selectivity obtained using only simple pinacol *Z*-crotyl boronate and a commercial C_2 symmetric diol as chiral ligand.


TBSO
O
H
1.36
+
O
B
O
1.37
(*R*,*R*) **1.35**
10 mol%
OH
TBSO
(77), 95:5 e.r.

Equation 1-14

1.5 Thesis goal

The unifying theme of this thesis is the development of a synthetically useful carbonyl allylation methodology using boron chemistry. In this regard, Chapter 2 describes work accomplished towards the development of an enantioselective Lewis acid-catalyzed allylboration. This chapter summarizes the screening of chiral diol auxiliaries in conjunction with Lewis acid catalysis, as well as the optimization of the Lewis acid itself. The substrate scope and generality are also described. The amenability of this method to larger scale is also explored. Finally a concise application of the methodology is described.

To render this enantioselective Lewis acid-catalyzed allylboration of aldehydes more accessible, two new syntheses of the necessary chiral diol auxiliary were developed. Thus, chapter 3 describes the optimization of each step in the two syntheses. One starts from the cheap starting material camphor and the other one, more direct, from camphorquinone. This chapter also reports useful observations made in the course of this work.

Attempts to extend the Lewis acid-catalyzed allylboration to more complex allylboration reagents are described in Chapter 4. In this chapter, the application of this catalytic manifold to α-silyl substituted allylboronates was carried out.

Efforts toward the synthesis of a mixed silyl-boron bis-allylation reagent are reported. This sub-project has proven to be an unexpectedly complex endeavor.

The power of the allylboration reaction presented in Chapter 2 of this thesis can only be displayed by its application to the synthesis of complex substances such as natural products. Thus, Chapter 5 presents our method in the context of the total synthesis of psymberin.

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Chapter 2

Enantioselective Catalytic Allylboration of Aldehydes

2.1 Introduction

Due to their synthetic appeal, allylboron reagents are still under intense investigation.[1] The discovery of the Lewis acid-catalyzed allylboration by Kennedy and Hall,[2] and others,[3] has revived significant interest in the class of stable and easy to handle allylboronate reagents. This new catalytic manifold provides the benefit of increased reactivity at lower temperatures, which significantly improves the substrate scope and the stereoselectivity of the reaction. It also opens the door to the development of new and improved catalytic methods for the allylboration of aldehydes. Indeed, a wide variety of aldehydes can be employed successfully in the allylboration reaction, including functionalized aliphatic aldehydes, which could be elaborated towards the synthesis of complex natural products. When we started this work, however, there were no chiral boronic esters known to afford practical levels of enantioselectivity (>95% ee) in additions of both allyl and crotyl boronates to achiral aldehydes.[1a]

2.2 Development

On the basis of the potential beneficial effect of a lower reaction temperature and the different mechanistic nature of the Lewis acid-catalyzed manifold, we revisited a number of known chiral diol auxiliaries for boronic acids. In our initial series of experiments, the allylation of benzaldehyde was investigated using various solvents, temperatures, and Lewis acids identified from our previous studies (Figure **2-1**).[2] A small set of allylboronates **2.1** derived from chiral diol precursors **a-e** were compared under these variables (Equation **2-1**).

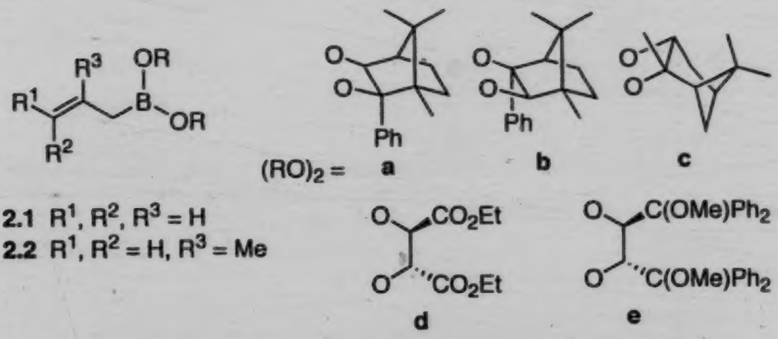
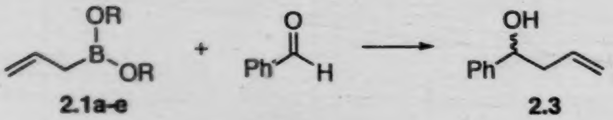


Figure 2-1 Structure of Investigated Chiral Diols

Using allylboronate (–)-**2.1a**, these investigations revealed that $Sc(OTf)_3$ provides the best combination of rate and enantioselectivity in the formation of homoallylic alcohol **2.3** (Table **2-1**, entries 1-7). A significant solvent effect was also observed, with dichloromethane standing out as the most efficient one both in terms of conversion and enantioselectivity (entries 7-12). Whereas pinanediol-based **2.1c** and the tartrate-based reagents **2.1d**[4] and **2.1e**[5] gave low enantioselectivity (entries 14-16), the Hoffmann camphor-derived allylboronates **2.1a** and **2.1b**[7] gave excellent results and, as reported by Hoffmann, provided inverse enantioselectivity (entries 7, 13). Further optimization revealed that the preferred order of addition involves first, suspending $Sc(OTf)_3$ in CH_2Cl_2 at –78 °C, followed by the aldehyde and a solution of the allylboronate in CH_2Cl_2. Any other combinations lead to lower yields or the presence of complex mixtures. Since in most cases the catalyst is only partially soluble, special care has to be put into the efficiency and consistency of the stirring. This is particularly true in the case of the best catalyst $Sc(OTf)_3$, where inconsistencies in stirring generated unreliable results. Furthermore, the addition of 4 Å molecular sieve did not improve the enantioselectivity (entry 8).



Equation 2-1

Table 2-1. Lewis Acid-Catalyzed Allylboration of Benzaldehyde[a]

entry	boronate	acid	solvent	Temp (°C)	conv.[b] (%)	ee[c] (%)
1[d]	**2.1a**	none	CH_2Cl_2	25	50	11
2	**2.1a**	$AlCl_3$	CH_2Cl_2	–78	14	63
3	**2.1a**	$TiCl_4$	CH_2Cl_2	–78	22	78
4	**2.1a**	TfOH	CH_2Cl_2	–78	72	84
5	**2.1a**	$Cu(OTf)_2$	CH_2Cl_2	–40	4	52
6	**2.1a**	$Yb(OTf)_3$	CH_2Cl_2	–40	4	38
7	**2.1a**	$Sc(OTf)_3$	CH_2Cl_2	–78	90	92
8[e]	**2.1a**	$Sc(OTf)_3$	CH_2Cl_2	–78	72	93
9	**2.1a**	$Sc(OTf)_3$	toluene	–78	30	46
10	**2.1a**	$Sc(OTf)_3$	hexanes	–78	20	8
11	**2.1a**	$Sc(OTf)_3$	Et_2O	–78	4	-
12	**2.1a**	$Sc(OTf)_3$	THF	–78	0	-
13	**2.1b**	$Sc(OTf)_3$	CH_2Cl_2	–78	62	84[f]
14	**2.1c**	$Sc(OTf)_3$	CH_2Cl_2	–78	100	9
15	**2.1d**	$Sc(OTf)_3$	CH_2Cl_2	–78	100	7
16	**2.1e**	$Sc(OTf)_3$	CH_2Cl_2	0	0	-

[a] Typical reaction conditions: 0.44 mmol of (–)-**2.1**, 0.40 mmol of benzaldehyde, 0.04 mmol of Lewis acid, 1 mL of solvent, –78 °C, 2 hours reaction time.

[b] Benzyl alcohol vs. benzaldehyde ^1H NMR signals after work-up.

[c] Measured by chiral HPLC.

[d] 72 hours reaction time.

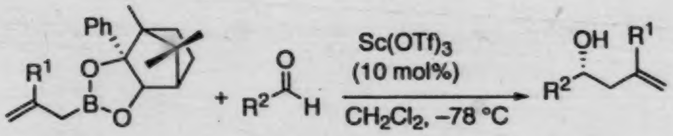
[e] 4 Å molecular sieves (10 mg) were added.

[f] The opposite enantiomer is predominant.

An important characteristic of Hoffmann's allylboronates is their relative stability. Indeed, they can be purified by chromatography and handled without any special precautions. Moreover, the diol precursor of allylboronate **2.1a** can be easily synthesized without any chromatographic purification in four steps from camphorquinone,[6] which is commercially available in both enantiomeric forms. The results obtained under our new catalytic manifold are in stark contrast with the enantioselectivity and the rate originally reported for the thermal uncatalyzed variant (see entry 1, without catalyst).[6]

2.3 Scope and limitations

Following the optimization of the reaction conditions, we next explored the generality of the reaction in terms of both the allylation reagent and the aldehyde partner. In the case of the allylboronate reagent, we wanted to know if the catalytic manifold could be extended to other allylation reagents, including the methallyl reagent (*E*- and *Z*-crotyl reagents will be discussed separately in section **2.6**). As shown in Table **2-2**, allylations of aromatic, aliphatic, and propargylic aldehydes using boronates **2.1a** and **2.2a** (Equation **2-2**) generally proceeded in good yields and very high enantioselectivities.



(+)-**2.1a** or **2.2a**

2.3-2.19

Equation 2-2

The simple allylation using **2.1a** (entries 1-9) smoothly provided homoallylic alcohols **2.3-2.11** and was usually completed within 4 hours, with the exception of α-branched aldehydes (entry 8) and the 2-decenaldehyde (entry 9). Although the lower enantioselectivity obtained with benzyl-protected hydroxyacetaldehyde was disappointing (entry 4), fortunately, its TBDMS-protected equivalent provided a satisfactory result (entry 5). Methallylation using **2.2a** also resulted in a very efficient process (entries 9-15), providing products **2.12-2.19**. Interestingly, this method represents one of the most efficient enantioselective methallylations of aldehydes to date, combining both substrate generality and high enantioselectivities.[1a]

Table 2-2. Substrate Scope for the $Sc(OTf)_3$-Catalyzed Addition of Allylboronates **2.1a** and **2.2a** to Aldehydes.

entry	boronate (R^1)	aldehyde (R^2)	product	yield (%)	ee (%)
1	**2.1a** (H)	Ph	**2.3**	85	92
2	**2.1a**	$PhCH_2CH_2$	**2.4**	64	97
3	**2.1a**	$TBDPSO(CH_2)_2$	**2.5**	86	93
4	**2.1a**	$BnOCH_2$	**2.6**	62	77
5	**2.1a**	$TBDMSOCH_2$	**2.7**	76	90
6	**2.1a**	$TBDPSOCH_2$	**2.8**	61	90
7	**2.1a**	$H_{11}C_5CC$	**2.9**	87	95
8	**2.1a**	C_6H_{11}	**2.10**	53	92
9	**2.1a**	*E*-$C_7H_{15}CHCH$	**2.11**	50	11
10	**2.2a** (Me)	Ph	**2.12**	64	98
11	**2.2a**	$PhCH_2CH_2$	**2.13**	76	97
12	**2.2a**	$TBDPSO(CH_2)_2$	**2.14**	77	97
13	**2.2a**	$BnOCH_2$	**2.15**	70	97
14	**2.2a**	$TBDMSOCH_2$	**2.16**	88	95
15	**2.2a**	$H_{11}C_5CC$	**2.17**	95	97
16	**2.2a**	C_6H_{11}	**2.18**	63	92
17	**2.2a**	*E*-$C_7H_{15}CHCH$	**2.19**	50	86

It was also found that α-branched aldehydes could undergo allylation with **2.1a** and **2.2a**, albeit at a slower rate (entries 8, 16)(reaction time 36 h vs.18 h). Additionally, we have discovered that propargylic aldehydes are excellent substrates for allylations using **2.1a** and **2.2a**. The application of our methodology to this class of substrates represents a complementary approach to the enantioselective addition of terminal alkynes to aldehydes, for which unstable β,γ-unsaturated aldehydes would be required.[7] Unfortunately, the reaction with alkenyl aldehydes is not performing as well as the alkynyl ones. In the case of the addition of allylboronate **2.1a** to (*E*)-2-decenal, the product **2.11** was obtained in moderate yield and low enantioselectivity, 50% and 11% respectively (entry 9). In the case of the methallylboronate **2.2a**, the product was obtained with a yield that was still moderate (50%) but the enantioselectivity was then increased to 86% (entry 17), which was acceptable. Interestingly, we noticed that the scandium catalyst exhibits very poor solubility in these reactions, suggesting the possibility of using a reduced catalyst loading, especially for reactions on a larger scale (vide infra).

In our original procedure, a DIBAL quench of the reaction mixture was followed by the addition of dilute acid. This standard workup procedure was required in order to eliminate any unreacted aldehyde before warming-up the reaction, and to hydrolyze the borate product formed in the reaction. Unfortunately, this procedure allowed for the recovery of only small amounts of the diol auxiliary (20-30%). The work-up step was optimized to incorporate a simple basic workup following the DIBAL quench, which led to a significantly improved recovery of the diol auxiliary. In a typical experiment, the reaction mixture was quenched by the addition of two equivalents of DIBAL and stirred at −78 °C for one hour. A 1 M aqueous solution of NaOH was then carefully added and followed by a liquid-liquid extraction with diethyl ether to provide a crude mixture containing both the homoallylic alcohol and the diol auxiliary. In this way, the diol auxiliary was cleanly cleaved from the borate product and did not show any sign of decomposition, as was the case with our previous acidic work-up. This recovered diol was then reused in the preparation of other batches of allylboronate without any loss in reactivity or selectivity. Additionally, any unreacted allylboronate was easily recovered and oxidized to maximize the recovery of the diol.[8] Since only one equivalent of diol auxiliary is generated from the reaction, the subsequent purification is simplified compared to other popular allylboron reagents. This is particularly true in the case of the Brown allylation where, after oxidative work-up, two equivalents of the alcohol coming from the oxidation of the isopinocampheyl groups are generated.[9] The presence of such a large amount of alcohol rendered the purification of the homoallylic alcohol very difficult.

2.4 Application

In order to test the practical potential of this system, we performed selected examples of allyl- and methallylborations on a gram-scale reaction. As can be seen from Table **2-3**, reagents **2.1a** and **2.2a** all gave satisfactory results on a preparative scale. These results are in line with the examples performed on a 0.4 mmol scale (see Table **2-2**). Most importantly, the diol auxiliary can be recovered in good yield in all cases for which the new basic workup was performed (entries 1-2 and 4). These results point out to the potential application of this methodology in natural product synthesis.

Table 2-3. Gram-Scale Addition of Allylboronates **2.1a** and **2.2a** to Aldehydes, According to Scheme **2-1**.

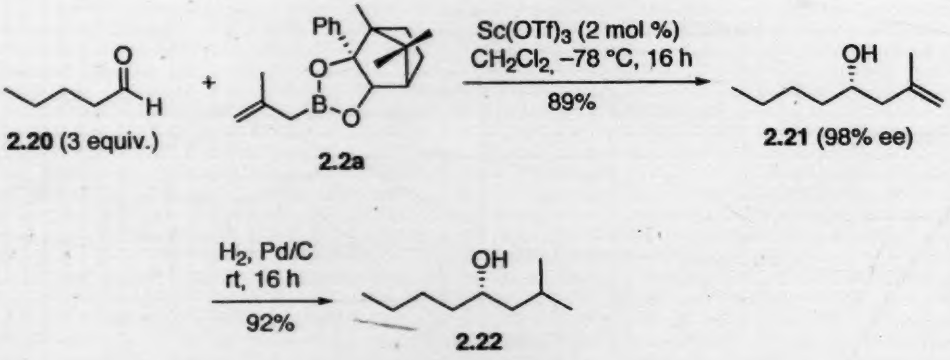
entry	boronate	product	yield (%)		ee (%)
			product[a]	diol[b]	
1	**2.1a**	**2.5**	65	78	97
2	**2.1a**	**2.9**	60	80	98
3	**2.2a**	**2.14**	71	-[c]	96
4	**2.2a**	**2.17**	95	65	97

[a] Yields of pure homoallylic alcohol products isolated after flash chromatography.

[b] Combined recovery yield of diol from the allylboration and the oxidation/hydrolysis of unreacted allylboronate.

[c] The original acidic workup was used and no diol isolation was attempted.

Accordingly, the usefulness of our methodology was tested towards a concise synthesis of (*S*)-(+)-2-methyl-4-octanol (**2.22**), the volatile male-produced aggregation pheromone of *Metamasius hemipterus* (Scheme **2-1**).[10] Allylation of pentanal (**2.20**) using boronate **2.2a** proceeded as expected, providing the homoallylic alcohol **2.20** in excellent yield (89%) and enantioselectivity (98% ee). In fact, the reaction proceeded smoothly with the use of only 2 mol % catalyst, a loading level at which the catalyst is still mostly insoluble. Standard hydrogenation of the olefin **2.21** gave access to the naturally occurring enantiomer of the pheromone in only 2 steps. This sequence represents the shortest enantioselective synthesis of (*S*)-(+)-2-methyl-4-octanol (**2.22**) to date.[11] This application also demonstrates the usefulness of boronates **2.1a** and **2.2a** for accessing aliphatic secondary alcohols that are difficult to synthesize through asymmetric reduction of the corresponding ketone precursors.



Scheme 2-1

2.5 Mechanistic considerations

On the basis of preliminary arguments presented earlier[2] and the fact that the diastereospecificity of the crotylation reactions is maintained, these Lewis acid-catalyzed allylboration reactions are thought to proceed through the usual closed chairlike transition state. Although the mode of activation has only been investigated for a similar system,[12] we propose activation of the boronate group via coordination of the scandium metal to one of the two exocyclic oxygen atoms (Figure **2-2**). The scandium$^{(III)}$ atom will most likely coordinate with the least hindered oxygen atom (i.e., the one away from the phenyl group), and furthermore, most probably with the least hindered of the two lone pairs (i.e., the one *syn* to the hydrogen). This coordination bond should increase the electrophilicity of the boron atom, a factor that was shown previously to be determinant in the reactivity of allylboron reagents.[13] The factors that determine the face selectivity remain unclear, although an attractive interaction between the aldehyde and the phenyl group has been proposed for related systems.[6,14] Further studies performed in our laboratories[12] are in agreement with this proposed mechanism for the Lewis acid-catalyzed allylboration reaction.

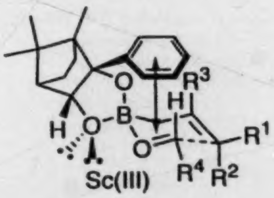
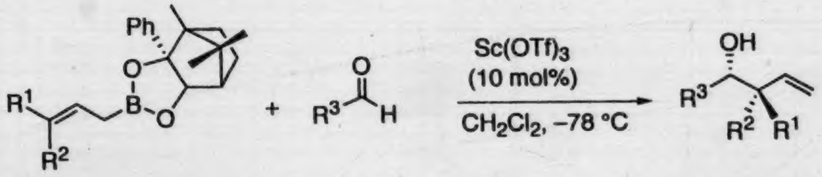


Figure 2-2 Proposed Transition State for the Enantioselective Sc(III)-Catalyzed Allylboration of Aldehydes

2.6 Application of Lewis acid-catalysis to *E*- and *Z*-crotylation

In our efforts to increase even more the generality of this new reaction, the enantioselective Lewis acid-catalyzed allylation was extended to the *E*- and *Z*-crotyl reagents (Equation **2-3**). This work was done by co-workers, Dr. Michel

Gravel and Dr. Xiaosong Lu. Although crotylborations using **2.23** and **2.24** were slower than allylations using **2.1a** or methallylations using **2.2a**, good yields can be obtained by simply using a small excess of either the boronate or the aldehyde. The enantioselectivity of these reactions is consistently good to excellent (90-97%) with the exception of the case of *Z*-crotylation of benzaldehyde; which provided the homoallylic alcohol in 59% enantiosectivity. As in the case of the allylation and methallylation reactions, these crotylation reactions were amenable to large scale (> 1 gram) with good recovery of the auxiliary.[15,16]



2.23, R^1 = Me, R^2 = H
2.24, R^1 = H, R^2 = Me

yield = 52-78%
ee = 90-97%

Equation 2-3

2.7 Conclusion

In summary, this newly developed method for the allylation of aldehydes brings a solution to some of the shortcoming of the current methods.[15,16] These hydrolytically stable camphordiol boronates can be purified by silica gel chromatography and manipulated without any particular precautions. Their reduced reactivity is counterbalanced by the addition of the external Lewis acid, which allows them to react even at –78 °C. These reagents are also suitable for addition to a wide range of functionalized aldehydes. We have shown the usefulness of this new catalytic manifold by reporting gram-scale examples with reproducible yield and selectivity, while achieving nearly quantitative recovery of the stochiometric chiral diol auxiliary. The application of this new reaction to the short and efficient synthesis of the male-produced aggregation pheromone of *Metamasius hemipterus* is a good example of its potential for natural product synthesis.

2.8 Experimental

2.8.1 General

Unless otherwise noted, all reactions were performed under an argon atmosphere using flame-dried glassware. Toluene, hexanes and CH_2Cl_2 were distilled over CaH_2. THF was distilled over sodium/benzophenone ketyl radical. All aldehydes were purified by bulb-to-bulb distillation prior to use. Boronates **2.1a** and **2.2a** were used within 24 hours after their purification. Thin layer chromatography (TLC) were performed on Merck Silica Gel 60 F254 plates and were visualized with UV light and 1% potassium permanganate/water ($KMnO_4$).

NMR spectra were recorded on Bruker AM 300, Bruker AM 200, Varian INOVA-300, INOVA-400 or INOVA-500 instrument. The residual solvent protons (^1H) or the solvent carbons (^{13}C) were used as internal standards for chemical shifts. Boron NMR spectra were referenced to external $BF_3 \cdot OEt_2$; ^{19}F spectra were referenced to external $CFCl_3$. Multiplicity is reported as s for singlet, d for doublet, t for triplet, q for quartet, and m for multiplet, whereby the prefix app is applied in cases where the true multiplicity is unresolved, and *br* when the signal in question is broadened, coupling constants (*J)* are given in hertz (Hz). In the case of ^{13}C NMR of boron containing compounds, the carbon directly attached to boron is not always observed due to the quadrupolar nature of the boron atom. High resolution mass spectra were recorded by the University of Alberta Mass Spectrometry Services Laboratory using either electron impact (EI) or electrospray (ES) ionization techniques. Infrared spectra were obtained on a Nicolet Magna-IR 750 instrument. Optical rotations were recorded using Perkin-Elmer PE-241. Elemental analyses were performed on a Carlo Erba CHNS-O EA1108 system. The enantiomeric excess for compounds **2.7**, **2.9**, **2.10**, **2.14**, **2.16-2.18**, and **2.21** was determined using integration of the ^{19}F NMR signals of the corresponding Mosher ester derivatives.[17] The enantiomeric excess for compounds **2.3-2.6**, **2.8**, **2.11-2.13**, **2.15**, and **2.19** was determined using an HP 1100 HPLC system. The enantiomeric excess for compounds **2.11** and **2.19** was determined on the corresponding phenylisocyanate adduct using an HP 1100 HPLC system. Chiralcel AD-RH, Chiralcel OD-RH, Chiralcel OD, and Chiralcel

AD columns were purchased from Chiral Technologies Inc. Racemic homoallylic alcohols were prepared either in the same manner using the pinacol boronate derivatives or through direct addition of the Grignard reagent on the aldehyde when possible

2.8.2 Preparation of allylboronates 2.1a and 2.2a

(1*R*,2*S*,3*R*,4*S*)-2,3-O-[Allylboryl]-2-phenyl-1,7,7-trimethylbornanediol (2.1a)[6]

To a solution of triisopropylborate (1.30 mL, 5.71 mmol) in Et_2O (12 mL) at –78 °C was added a solution of allylmagnesium bromide (1.02 M in Et_2O, 5.00 ml, 5.10 mmol) dropwise and the resulting mixture was stirred at –78 °C for 4 hours. The resulting suspension was poured onto an ice-cold mixture of 1 N HCl (50 mL), Et_2O (50 mL), and (1*R*,2*S*,3*R*,4*S*)-2-phenyl-1,7,7-trimethylbornanediol (**a**)[6] (980 mg, 3.98 mmol). The resulting mixture was stirred at ambient temperature for 30 minutes, then extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Flash chromatography (10% EtOAc/hexanes) yielded a colourless oil (1.104 g, 93%).

TLC (15% EtOAc/hexanes, $KMnO_4$): 0.70;

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.25 (m, 5H), 5.91-5.77 (m, 1H), 4.98-4.88 (m, 2H), 5.11 (d, *J* = 10.0 Hz, 1H), 4.73 (s, 1H), 2.15 (d, *J* = 5.2 Hz, 2H), 1.88-1.81

(m, 1H), 1.71 (d, *J* = 7.5 Hz, 2H), 1.23 (s, 3H), 1.19-1.14 (m, 2H), 1.08-1.01 (m, 2H), 0.97 (s, 3H), 0.94 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 141.8, 134.0, 127.5, 127.3, 126.8, 114.8, 95.8, 88.7, 52.1, 50.3, 48.9, 29.7, 24.8, 23.6, 20.8, 9.4;

^{11}B NMR (128 MHz, $CDCl_3$): δ 33.7.

(1*R*,2*S*,3*R*,4*S*)-2,3-O-[2-Methylallylboryl]-2-phenyl-1,7,7-trimethylbornanediol (2.2a)

To a solution of triisopropylborate (1.50 mL, 6.60 mmol) in Et_2O (12 ml) was added (1*R*,2*S*,3*R*,4*S*)-2-phenyl-1,7,7-trimethylbornanediol **(a)**[6] (1.48 g, 6.00 mmol). The mixture was stirred at ambient temperature for 30 minutes, then concentrated on the rotary evaporator and co-evaporated with CH_2Cl_2 (3 × 5 mL). The remaining colorless oil was dissolved in Et_2O (12 ml) and cooled to –78 °C. To this solution was added a solution of 2-methylallylmagnesium chloride (0.5 M in THF, 12.6 mL, 6.3 mmol). The resulting suspension was stirred at –78 °C for 4 hours, then poured on an ice-cold mixture of 1 N HCl (50 mL) and Et_2O (50 ml). The resulting mixture was stirred at ambient temperature for 30 minutes, then extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Flash chromatography (10% EtOAc/hexanes, SiO_2 pre-treated with 5% Et_3N/hexanes) yielded a colorless oil (1.31 g, 70%).

TLC (15% EtOAc/hexanes, $KMnO_4$): 0.60;

$[\alpha]^{25}_D$ +24.3 (c = 2.16, $CHCl_3$);

^1H NMR (300 MHz, $CDCl_3$): δ 7.44-7.41 (m, 2H), 7.37-7.25 (m, 3H), 4.73 (s, 1H), 4.62 (dd, J = 1.9, 1.4 Hz, 1H,), 4.57 (d, J = 0.8 Hz, 1H), 1.88-1.76 (m, 1H), 1.75 (dd, J= 1.4, 0.8 Hz, 3H), 1.71 (s, 2H), 1.24 (s, 3H), 1.27-1.14 (m, 2H), 1.08-0.98 (m, 1H), 0.96 (s, 3H), 0.94 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 142.8, 141.8, 127.5, 127.3, 126.8, 124.8, 110.0, 100.5, 95.8, 88.7, 52.0, 50.2, 48.9, 29.6, 24.8, 24.4, 23.6, 20.9, 9.4.

^{11}B (128 MHz, $CDCl_3$): δ 33.6;

IR (CH_2Cl_2 cast, cm^{-1}): 3072, 2957, 1646, 1445, 1338, 1034;

HRMS (EI, *m/z*) Calcd for $C_{20}H_{27}O_2B$: 310.2104. Found: 310.2111;

Anal. Calcd for $C_{20}H_{27}O_2B$: C, 77.43; H, 8.77. Found: C, 77.40; H, 8.85.

2.8.3 General procedure for the synthesis of homoallylic alcohols 2.3-2.19

Scandium trifluoromethanesulfonate (16 mg, 0.03 mmol) and CH_2Cl_2 (1.5 mL) were introduced in a round-bottom flask under N_2 atmosphere, and the mixture was cooled to –78 °C. The aldehyde (0.33 mmol) was added, followed by a solution of boronate **2.1a** or **2.2a** (0.36 mmol) in CH_2Cl_2 (0.5 mL) dropwise over 5 minutes. The resulting mixture was stirred at –78 °C for 16 hours, then DIBAL (1.0 M in toluene, 0.66 mL, 0.66 mmol) was added. The mixture was stirred at –78 °C for 30 minutes, then 1 N HCl (5 mL) was carefully added and the flask was allowed to warm up to ambient temperature. The resulting layers were separated, then the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated. Flash chromatography (5% EtOAc/hexanes) afforded the pure homoallylic alcohol.

(1*R*)-1-phenyl-3-buten-1-ol (2.3)[18]

Colourless oil (41 mg, 85%).

TLC (15% EtOAc/hexanes, $KMnO_4$): 0.23;

^1H NMR (300 MHz, $CDCl_3$): δ 7.35-7.22 (m, 5H), 5.78 (dddd, *J* = 17.2, 10.3, 7.5, 7.5 Hz, 1H), 5.18-5.10 (m, 2H), 4.74 (dd, *J* = 7.5, 5.4 Hz, 1H), 2.51-2.45 (m, 2H), 1.98 (br s, 1H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 143.7, 134.3, 128.2, 127.3, 125.7, 118.0, 73.1, 43.6;

HPLC: Chiralcel OD-RH, 40% *i*-PrOH/H_2O, 0.40 mL/min., UV detection at 210 nm, major peak at 22.3 min., minor peak at 25.7 min., 92% ee.

(3*S*)-1-phenyl-5-hexen-3-ol (2.4)[18]

Colourless oil (37 mg, 64%).

TLC (15% EtOAc/hexanes, $KMnO_4$): 0.25;

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.18 (m, 5H), 5.89-5.74 (m, 1H), 5.16 (br s, 1H), 5.11 (br s, 1H), 3.69-3.63 (m, 1H), 2.85-2.62 (m, 2H), 2.35-2.12 (m, 2H), 1.82-1.25 (m, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 142.0, 134.6, 128.4, 128.3, 125.8, 118.3, 69.9, 42.0, 38.4, 32.0;

HPLC: Chiralcel OD-RH, 40% *i*-PrOH/H_2O, 0.40 mL/min., UV detection at 210 nm, major peak at 40.2 min., minor peak at 49.4 min., 97% ee.

(3*R*)-1-(*t*-Butyldiphenylsilyloxy)-5-hexen-3-ol (2.5)[19]

Colourless oil (79 mg, 86%).

TLC (15% EtOAc/ hexanes, $KMnO_4$): 0.30;

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, *J* = 7.2 Hz, 4H), 7.47-7.37 (m, 6H), 5.92-5.78 (m, 1H), 5.13-5.08 (m, 2H), 4.00-3.92 (br m, 1H), 3.92-3.79 (m, 2H), 3.18 (br s, 1H), 2.26 (t, *J* = 6.0 Hz, 2H), 1.77-1.64 (m, 2H), 1.05 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 135.5, 134.9, 133.1, 129.8, 127.8, 117.4, 70.9, 63.3, 42.0, 37.8, 26.8, 19.0;

HPLC: Chiralcel AD-RH, 45% *i*-PrOH/H_2O, 0.40 mL/min., UV detection at 210 nm, major peak at 60.8 min., minor peak at 67.8 min., 93% ee.

(2*R*)-1-(Benzyloxy)-4-penten-2-ol (2.6)[19]

Colourless oil (39 mg, 62%).

TLC (15% EtOAc/toluene, $KMnO_4$): 0.15;

^{1}H NMR (300 MHz, CDCl$_3$): δ 7.36-7.29 (m, 5H), 5.89-5.78 (m, 1H), 5.14-5.08 (m, 2H), 4.58 (s, 2H), 3.90-3.81 (m, 1H), 3.50 (dd, *J* = 10.1, 3.7 Hz, 1H), 3.37 (dd, *J* = 9.1, 7.3 Hz, 1H), 2.25 (m, 3H);

^{13}C NMR (125 MHz, CDCl$_3$): δ 137.9, 134.2, 128.4, 127.8, 126.8, 117.7, 73.9, 73.4, 69.7, 37.9;

HPLC: Chiralcel OD, 2% *i*-PrOH/hexane, 0.40 mL/min., UV detection at 210 nm, major peak at 49.3 min., minor peak at 52.5 min., 77% ee.

(2*R*)-1-(*t*-Butyldimethylsilyloxy)-4-penten-2-ol (2.7)[19]

Colourless oil (54 mg, 76%).

TLC (15% EtOAc/hexanes, KMnO$_4$): 0.40;

^{1}H NMR (300 MHz, CDCl$_3$): δ 5.90-5.78 (m, 1H), 5.13-5.04 (m, 2H), 3.82-3.63 (m, 1H), 3.20 (dd, *J* = 10.7, 4.1 Hz, 1H), 3.44 (dd, *J* = 10.7, 5.9 Hz, 1H), 2.36, (br s, 1H), 2.24 (t, *J* = 7.2 Hz, 2H), 0.92 (s, 9H), 0.07 (s, 6H);

^{13}C NMR (100 MHz, CDCl$_3$): δ 134.4, 117.4, 71.2, 66.6, 37.7, 26.0, 18.3, -5.2;

^{19}F NMR (376 MHz, CDCl$_3$): δ –71.90 (major), –71.99 (minor) 90% ee on the Mosher ester derivative.[17]

(2*R*)-1-(*t*-Butyldiphenylsilyloxy)-4-penten-2-ol (2.8)[19]

Colourless oil (69 mg, 61%).

TLC (15% EtOAc/hexanes, KMnO$_4$): 0.25;

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, *J* = 7.2 Hz, 4H) 7.47-7.37 (m, 6H), 5.92-5.78 (m, 1H), 5.13-5.08 (m, 2H), 3.84-3.72 (m, 1H), 3.66 (dd, *J* = 10.1, 3.8 Hz, 1H), 3.55 (dd, *J* = 10.1, 5.9 Hz, 1H), 2.43 (br s, 1H), 2.25 (app t, *J* = 6.5 Hz, 2H), 1.05 (m, 9H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 135.5, 134.3, 133.2, 129.7, 127.8, 117.4, 71.3, 67.4, 37.6, 26.8, 19.2;

HPLC: Chiralcel AD-RH, 45% *i*-PrOH/H_2O, 0.33 mL/min., UV detection at 210 nm, major peak at 75.1 min., minor peak at 88.4 min., 90% ee.

(4*R*)-1-Undecen-5-yn-4-ol (2.9)[20]

Colourless oil (48 mg, 87%).

TLC (15% EtOAc/toluene, $KMnO_4$): 0.20;

$[\alpha]^{25}_D$ +22.4 (*c* = 6.8, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.94-5.73, (m, 1H), 5.24-5.15 (m, 2H), 4.40 (m, 1H), 2.42 (t, *J* = 7.0 Hz, 2H), 2.20 (td, *J* = 7.0, 2.0 Hz, 2H), 1.77 (br s, 1H), 1.58-1.42 (m, 2H), 1.42-1.25 (m, 4H), 0.87 (m, 3H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 133.3, 118.7, 86.0, 80.5, 61.8, 42.6, 31.0, 28.3, 22.2, 18.6, 13.9;

IR (CH_2Cl_2 cast, cm^{-1}): 3354, 3078, 2957, 2932, 2860, 1642, 1467, 1432, 1379, 1331, 1143;

HRMS (ES, *m/z*) Calcd for $C_{11}H_{18}ONa$: 189.1250. Found: 189.1250;

^{19}F NMR (376 MHz, $CDCl_3$) δ –71.95 (major), –72.18 (minor) 98% ee on the Mosher ester derivative.[17]

(1*R*)-1-(Cyclohexyl)-3-buten-1-ol (2.10)[21]

Colourless oil (26 mg, 53%).

TLC (15% EtOAc/toluene, $KMnO_4$): 0.30;

$[\alpha]^{25}_{D}$ –0.91 (*c* = 0.8, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.90-5.79 (m, 1H), 5.17-5.12 (m, 2H), 3.42 (ddd, *J* = 9.0, 4.8, 3.5 Hz,1H), 2.37-2.30 (m, 1H), 2.17-2.09 (m, 1H), 1.89-1.65 (m, 5H), 1.54 (br s, 1H), 1.40-0.87 (m, 6H);

^{19}F NMR (376 MHz, $CDCl_3$) δ –71.53 (minor), –71.59 (major), 90% ee on the Mosher ester derivative.

Dodeca-1,5-dien-4-ol (2.11)[22]

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.90-5.65 (m, 2H), 5.50-5.41 (m, 1H), 5.17-5.12 (m, 2H), 4.14. (dd, *J* = 6.6, 6.6 Hz, 1H), 2.37-2.22 (m, 2H), 2.05 (q, *J* = 6.4 Hz, 2H), 1.76 (br s, 1H), 1.40-1.27 (m, 8H), 0.87 (t, *J* = 6.6 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 134.6, 132.3, 131.9, 118.0, 71.7, 42.1, 32.1, 31.7, 29.2, 28.8, 22.6, 14.1;

HPLC: Performed on the isocyanate derivative, Chiralcel OD, 95% Hexane/*i*-PrOH, 1.0 mL/min., UV detection at 210 nm, major peak at 7.8 min., minor peak at 13.4 min., 10% ee.

(1*R*)-3-Methyl-1-phenyl-3-buten-1-ol (2.12)[18]

Colourless oil (30 mg, 64%).

TLC (15% EtOAc/hexanes, $KMnO_4$): 0.25;

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42-7.22 (m 5H), 4.94 (m, 1H), 4.86 (m, 1H), 4.83 (td, *J* = 6.8, 2.4 Hz, 1H), 2.43 (dd, *J* = 6.8, 0.9 Hz, 2H), 2.31 (s, 1H), 1.82 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 144.0, 142.4, 128.4, 127.4, 125.7, 114.0, 71.4, 48.4, 22.3;

HPLC: Chiralcel AD-RH, 50% *i*-PrOH/H_2O, 0.31 mL/min., UV detection at 210 nm, major peak at 18.0 min., minor peak at 20.2 min., 98% ee.

(3*R*)-5-Methyl-1-phenyl-5-hexen-3-ol (2.13)[18]

(Made from the enantiomer of **2.2a**)

Colourless oil (44 mg, 76%).

TLC (15% EtOAc/hexanes, $KMnO_4$): 0.25;

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.17 (m, 5H), 4.91 (s, 1H), 4.81 (s, 1H), 3.83-3.74 (m, 1H), 2.90-2.65 (m, 2H), 2.30-2.10 (m, 2H), 1.84-1.70 (m, 6H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 142.6, 142.1, 128.4, 128.3, 125.8, 113.6, 68.0, 46.2, 38.8, 32.1, 22.4;

HPLC: Chiralcel OD-RH, 45% *i*-PrOH/H_2O, 0.4 mL/min., UV detection at 210 nm, minor peak at 35.0 min., major peak at 39.9 min., 97% ee.

(3*S*)-1-(*t*-Butyldiphenylsilyloxy)-5-methyl-5-hexen-3-ol (2.14)

Colourless oil (90 mg, 77%).

TLC (15% EtOAc/hexanes, $KMnO_4$): 0.30;

$[\alpha]^{25}_D$ +0.89 (c = 1.23, $CHCl_3$);

^1H NMR (300 MHz, $CDCl_3$): δ 7.70-7.67 (m, 4H), 7.44-7.39 (m, 6H), 4.84 (dd, J = 3.7, 1.5 Hz, 1H), 4.57 (d, J = 0.8 Hz, 1H), 4.09-4.03 (m, 1H), 3.94-3.80 (m, 2H), 2.96 (d, J = 2.4 Hz, 1H), 2.29-2.14 (m, 2H), 1.77 (s, 3H), 1.76-1.68 (m, 2H), 1.06 (s, 9H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 142.7, 135.5, 133.2, 129.7, 127.7, 112.9, 68.6, 62.9, 46.0, 38.3, 26.8, 22.5, 19.1;

IR (CH_2Cl_2 cast, cm^{-1}): 3455, 3049, 2931, 1472, 1427, 1111;

HRMS (EI, *m/z*) Calcd for $C_{23}H_{32}O_2NaSi$: 391.2064. Found: 391.2064;

^{19}F NMR (376 MHz, $CDCl_3$) δ −71.69 (major), −71.79 (minor) 97% ee on the Mosher ester derivative.[17]

(2*R*)-1-(Benzyloxy)-4-methyl-4-penten-2-ol (2.15)

Colourless oil (46 mg, 70%).

TLC (15% EtOAc/hexanes, $KMnO_4$): 0.15;

$[\alpha]^{25}_D$ −1.86 (c = 1.30, $CHCl_3$);

^1H NMR (300 MHz, $CDCl_3$): δ 7.36-7.26 (m, 5H), 4.83 (dd, J = 1.7, 1.7 Hz, 1H), 4.76 (dd, J = 1.0, 1.0 Hz, 1H), 4.55 (s, 2H), 3.99-3.95 (m, 1H), 3.50 (dd, J = 9.5, 3.5 Hz, 1H), 3.37 (dd, J = 9.5, 7.1 Hz, 1H), 2.27 (d, J = 2.9 Hz, 1H), 2.22-2.16 (m, 2H), 1.75 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 142.0, 138.0, 128.4, 127.8, 127.7, 113.2, 74.2, 73.4, 68.2, 41.9, 22.5;

IR (CH_2Cl_2 cast, cm^{-1}): 3445, 3070, 3030, 2913, 1646, 1453, 1099;

HPLC: Chiralcel OD-RH, 65% *i*-PrOH/H_2O, 0.45 mL/min., UV detection at 210 nm, minor peak at 52.7 min., major peak at 55.9 min., 97% ee.

(2*R*)-1-(*t*-Butyldimethylsilyloxy)-4-methyl-4-penten-2-ol (2.16)

Colourless oil (67 mg, 88%).

TLC (15% EtOAc/toluene, $KMnO_4$): 0.40;

$[\alpha]^{25}_D$ −1.86 (c = 1.30, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.81 (dd, J = 1.4, 1.4 Hz, 1H), 4.76 (dd, J = 2.0, 1.0 Hz, 1H), 3.81-3.77 (m, 1H), 3.60 (dddd, J = 10.0, 4.8, 3.9, 0.9 Hz, 1H), 3.45 (dd, J = 10.0, 7.0 Hz, 1H), 2.33 (d, J = 2.9 Hz, 1H), 2.15 (d, J = 6.8 Hz, 2H), 1.75 (s, 3H), 0.89 (s, 9H), 0.06 (s, 6H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 142.3, 112.9, 69.7, 66.9, 41.7, 26.0, 22.7, 18.4, -5.1, -5.2;

IR (CH_2Cl_2 cast, cm^{-1}): 3467, 3076, 2955, 2929, 1648, 1472, 1361, 1120;

^{19}F NMR (376 MHz, $CDCl_3$) δ −71.91 (major), −71.99 (minor) 95% ee on the Mosher ester derivative.[17]

General procedure for the gram-scale synthesis of homoallylic alcohols, synthesis of 2.17

Scandium trifluoromethanesulfonate (58 mg, 0.12 mmol, 0.02 equiv) and CH_2Cl_2 (5 mL) were introduced in a 50-mL round-bottom flask, and the mixture was cooled to –78 °C. 2-Octynal (0.836 mL, 5.87 mmol) was added, followed by a solution of boronate **2.2a** (2.00 g, 4.83 mmol) in CH_2Cl_2 (7 mL) dropwise over 30 minutes. The resulting mixture was stirred at –78 °C for 24 hours, then DIBAL (1.0 M in toluene, 12.8 mL, 12.8 mmol) was added. The mixture was stirred at –78 °C for 1 hour, then carefully poured into a 250-mL separatory funnel containing 1 N NaOH (50 mL). The resulting layers were separated, then the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Flash chromatography (5% EtOAc/hexanes) afforded homoallylic alcohol **2.17** as a colourless oil (1.06 mg, 95%). The fractions containing the diol auxiliary and the ones containing diol-boronate derivatives were concentrated, then treated with a solution of THF (2 mL), 1 N NaOH (1 mL), and H_2O_2 (1 mL of a 30% aqueous solution) for 16 hours. The resulting mixture was diluted with water (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Flash chromatography (5% EtOAc/hexanes) afforded (1*R*,2*S*,3*R*,4*S*)-2-phenyl-1,7,7-trimethylbornanediol (**a**) (900 mg, 65%).

(4*R*)-2-Methyl-1-undecen-5-yn-4-ol (2.17)

(Performed on a 5.87 mmol scale)

Colourless oil (1.06 g, 95%).

TLC (15% EtOAc/toluene, $KMnO_4$): 0.20;

$[\alpha]^{25}_{D}$ +35.2 (c = 8.0, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.9 (dd, J = 1.9, 1.9 Hz, 1H), 4.84 (dd, J = 1.0, 1.0 Hz, 1H), 4.54-4.41 (m, 1H), 2.44 (d, J = 7.0 Hz, 2H), 2.20 (td, J = 7.0, 1.0 Hz, 2H), 1.80 (s, 3H), 1.60-1.25 (m, 7H), 0.87 (t, J=7.1 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 141.3, 114.7, 85.7, 80.7, 60.6, 46.5, 31.0, 28.3, 22.6, 22.2, 18.6, 13.9;

IR (CH_2Cl_2 cast, cm^{-1}): 3362, 3076, 2957, 2932, 1648, 1456, 1377, 1330, 1137;

HRMS (ES, *m/z*) Calcd for $C_{12}H_{20}ONa$: 203.1406. Found: 203.1408;

^{19}F NMR (376 MHz, $CDCl_3$) δ –71.92 (major), –72.07 (minor) 97% ee on the Mosher ester derivative.[17]

(1*R*)-1-(Cyclohexyl)-3-buten-1-ol (2.18)[23]

Colourless oil (35 mg, 63%).

TLC (15% EtOAc/toluene, $KMnO_4$): 0.30;

$[\alpha]^{25}_{D}$ –0.82 (c = 2.7, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.91 (s, 1H), 4.82 (s, 1H), 3.52-3.43 (m, 1H), 2.32-2.05 (m, 2H), 1.95-1.63 (m, 6H), 1.78 (s, 3H), 1.44-1.00 (m, 6H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 143.3, 113.4, 72.5, 43.0, 29.1, 28.2, 26.6, 26.3, 22.2;

^{19}F NMR (376 MHz, $CDCl_3$) δ –71.53 (minor), –71.69 (major), 92% ee on the Mosher ester derivative.[17]

2-Methyl-dodeca-1,5-dien-4-ol (2.19)

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.70 (dtd, *J* = 15.3, 6.7, 1.0 Hz, 1H), 5.48 (ddt, *J* = 15.3, 6.6, 1.4 Hz, 1H), 4.89-4.87 (m, 1H), 4.82-4.80 (m, 1H), 4.21 (app q, *J* = 6.6, 1H), 2.23 (dd, *J* = 6.9, 1.0 Hz, 2H), 2.03 (q, *J* = 6.7, 2H), 1.78-1.77 (m, 3H), 1.67 (d, *J* = 2.9 Hz, 1H), 1.40-1.27 (m, 8H), 0.89 (t, *J* = 6.2 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 142.3, 132.2, 132.1, 113.6, 70.1, 46.3, 32.2, 31.7, 29.1, 28.8, 22.6, 22.5, 14.1;

IR (Neat film, cm^{-1}): 3371, 3074, 2957, 2926, 2855;

HRMS (ES, *m/z*) Calcd for $C_{13}H_{24}ONa$: 219.1719. Found: 219.1721;

HPLC: Performed on the isocyanate derivative, Chiralcel OD, 95% Hexane/*i*-PrOH, 1.0 mL/min., UV detection at 250 nm, minor peak at 6.6 min., major peak at 7.5 min., 86% ee.

2.8.4 Synthesis of (*S*)-(+)-2-methyl-4-octanol (2.22)

(*S*)-(−)-2-Methyl-1-octen-4-ol (2.21)[24]

Same procedure used as for homoallylic alcohols **2.5-2.21** using boronate **2.2a**, on a 2.0 mmol scale and using 3.0 equiv. of pentanal (**2.20**).

Volatile colourless oil (257 mg, 89%).

TLC (15% EtOAc/toluene, $KMnO_4$): 0.30;

$[\alpha]^{25}_{D}$ −9.2 (c = 0.65, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.88 (s,1H), 4.80 (s, 1H), 3.77-3.67 (m, 1H), 2.30-2.06 (m, 2H), 1.78 (s, 3H), 1.65 (br s, 1H), 1.55-1.25 (m, 6H), 0.92 (t, J = 7.0 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 142.9, 113.3, 68.6, 46.2, 36.8, 27.9, 22.7, 22.4, 14.0;

^{19}F NMR (376 MHz, $CDCl_3$) δ −71.60 (minor), −71.69 (major), 98% ee on the Mosher ester derivative.[17]

(*S*)-(+)-2-Methyl-4-octanol (2.22)[11]

In a flame-dried round bottom flask, alcohol **2.23** (144 mg, 1.0 mmol) was dissolved in methanol (1.0 mL). Palladium on charcoal (10 mol %, 10 mg) was added, and the resulting suspension was stirred for 16 hours at room temperature under an atmosphere of H_2. The suspension was then filtered on celite and diluted with pentane (5 mL). The solution was washed with water (3 × 5 mL), dried over magnesium sulfate, filtered and concentrated. Flash chromatography (5% EtOAc/hexanes) yielded a volatile colourless oil (135 mg, 92%).

TLC (15% EtOAc/Toluene, $KMnO_4$): 0.35;

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.70-3.65 (m, 1H), 1.83-1.75 (m, 1H), 1.50-1.20 (m, 8H), 0.95-0.85 (m, 9H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 70.0, 46.9, 34.1,27.2, 24.6, 23.4, 22.7, 22.3, 14.0.

2.9 References

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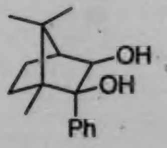
Chapter 3

New Syntheses of the Camphor-Derived Diol Auxiliary

3.1 Introduction

For many years, the selective formation of new carbon-carbon bonds has been the driving force behind many discoveries in organic chemistry. In many of the successful stereocontroled processes, a chiral diol is used either as a chiral ligand or a chiral auxiliary.[1] Whereas the use of both natural and synthetic C_2 symmetric diols is widespread, the use of non-C_2 symmetric diols is not as common due to the limited number of naturally occurring diols such as pinanediol. Many of these chiral diols have been applied to the allylation of carbonyl compounds and contributed to making this reaction one of the most successful methods in the domain of stereoselective carbon-carbon bond formation.[2]

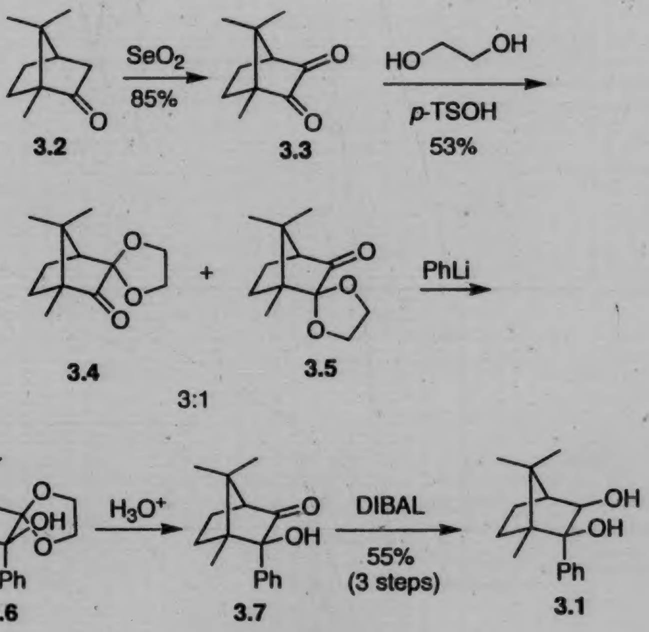
In the previous chapter, the work on a new enantioselective Lewis acid-catalyzed allylboration of aldehydes was described.[3,4] This new catalytic allylboration manifold affords excellent enantio- and diastereoselectivities, along with moderate to good yields of products. The camphor-derived diol allylboronates used in this method tolerate a wide range of conditions, such as air, moisture, and silica gel chromatography, thereby solving many of the shortcomings of the previously mentioned methods (see section **1.4.1**). The main drawback of this method is the use of a complex chiral auxiliary. By today's standards, this is a major limitation that will prevent other groups from using our methodology. Even with all the success achieved with the new catalytic manifold, if the auxiliary is not readily available or commercial, people will preferentially use other methods using more accessible reagents. The required camphor-derived diol precursor, (–)-(1*R*,2*R*,3*R*,4*S*)-1,7,7-trimethyl-2-phenyl-bicyclo[2.2.1]heptane-2,3-diol (**3.1**), was originally synthesized[5] in five steps (Scheme **3-1**) from camphor (**3.2**) with a maximum overall yield of 25%. Four of these steps each required a reaction time of over 18 hours.



3.1

Figure 3-1 Structure of the Camphor-Derived Diol **3.1**

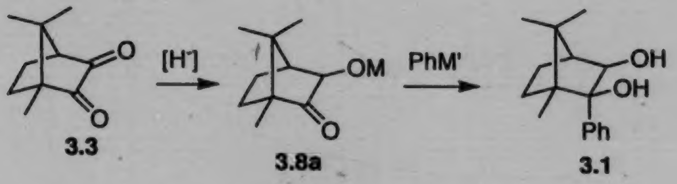
These limitations prompted us to look for a more efficient route to access the Hoffmann camphor-derived diol **3.1**. The synthetic usefulness of this diol in the Lewis acid-catalyzed allylboration reaction, as well as its possible application to other reactions made the development of an improved synthetic route a worthwhile endeavor. To be viable, the new route would have to be short (fewer steps and shorter reaction time), quick and easy to execute, and amenable to multigram scale synthesis of diol **3.1**.



Scheme 3-1

The original synthesis of Hoffmann and co-workers[5] of **3.1** begins with a selenium dioxide oxidation[6] of camphor (**3.2**). In our hands, this reaction provided the desired product, which consistently contained 4-10% of unreacted camphor. This residual camphor was not easily removed from the product. Another drawback of this synthetic route was the acetal formation step,[7] which consistently gave rise to a 3:1 mixture in favor of the desired product **3.4** over regioisomer **3.5**, resulting in a significant loss of material.

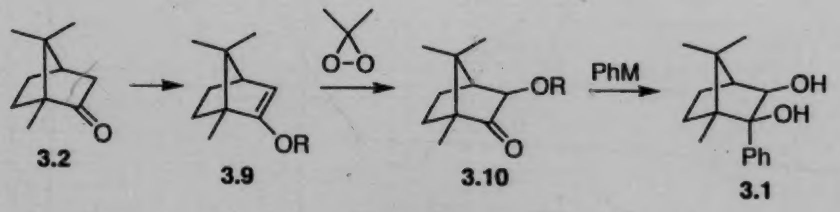
Two possible alternate routes to access diol **3.1** were envisaged. Route A (Scheme **3-2**), starting from compound **3.3**, was an attempt to circumvent the protection and deprotection steps of the original synthesis by performing a selective reduction of the least hindered ketone.[8] By avoiding the protection step, the loss of one quarter of the material due to the low selectivity of the protection step would be prevented, thus increasing the overall yield. The resulting reaction mixture, containing the more hindered unreacted ketone, would then be submitted to the addition of a phenyl-metal reagent to afford diol **3.1**.



Scheme 3-2

Route B (Scheme **3-3**) made use of camphor (**3.2**) as a significantly cheaper raw material, which would be first converted to its enol ether, then oxidized by dimethyldioxirane (DMDO),[9] followed by the addition of a phenyl-metal species.

Like Route A, this proposed route would also circumvent the protection problem of the current synthesis.

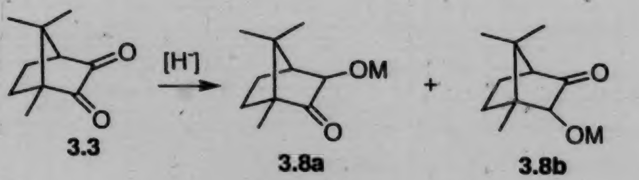


Scheme 3-3

3.2 Synthesis from camphorquinone (3.3)

In the development of Route A, we first investigated the nature of the reducing agent (Equation **3-1**), including common reagents such as DIBAL and Red-Al® as well as reagents known to be more sensitive to steric bulk such as L-Selectride®, $LiAlH(O\text{-}t\text{-}Bu)_3$, and $LiBH(Et)_3$. The effect of solvent and temperature was also investigated, as well as the rate of addition. The results of these experiments are summarized in Table **3-1**. As seen in entries 1 and 2, the most common reducing agents afforded no selectivity at all, gave rise to low yields or unselective reduction of the carbonyls ($LiAlH(O\text{-}t\text{-}Bu)_3$, and $LiBH(Et)_3$). Furthermore, in the case of Red-Al®, a complex mixture of products was obtained, including the fully reduced product. In the case of the more sterically sensitive reagents, L-Selectride® was found to be markedly more selective than $LiAlH(O\text{-}t\text{-}Bu)_3$ or $LiBH(Et)_3$.

The importance of controlling the rate of addition is demonstrated by entry 9, in which the ratio of the desired product rises from 7:1 to >9:1 when L-Selectride® was added over a period of 40 minutes. In the investigation on the solvent effect, THF was shown to be a significantly better solvent than ether (entries 9 and 10). THF afforded a much greater ratio of desired product than in the case of ether (9:1 vs. 5:1). The product obtained under the best conditions (slow addition of L-Selectride® at 0 °C), was used without any further purification in the following arylation step.



3.3 3.8a 3.8b

Equation 3-1

Table 3-1. Optimization of Reduction Conditions for Camphorquinone (**3.3**), Route A.[a]

entry	hydride source [H⁻]	temp (°C)	**3.8a: 3.8b**[b]	yield (%)
1	DIBAL	0	1:1	-[c]
2	Red-Al®	0	[d]	-[c]
3[e]	$LiAlH(O\text{-}t\text{-}Bu)_3$	0	3:2	83
4[f]	$LiAlH(O\text{-}t\text{-}Bu)_3$	0	3:1	-[c]
5[e]	$LiAlH(O\text{-}t\text{-}Bu)_3$	–40	4:3	51
6	$LiBH(Et)_3$	0	3:2	49
7	$LiBH(Et)_3$	–40	3:2	-[c]
8	L-Selectride®	0	7:1	-[g]
9	L-Selectride®	0	9:1[h]	-[g]
10	L-Selectride®	0	5:1[i]	-[c]

[a] Reactions were performed in THF with 1 equiv of hydride reagent added over 10 min as their commercially available solution; reactions were worked-up using 1M HCl (aq).

[b] Ratio determined by ^{1}H NMR of the crude reaction mixture.

[c] Product not isolated.

[d] Reduction of both carbonyls was observed.

[e] $LiAlH(O\text{-}t\text{-}Bu)_3$ was added portion-wise as a solid.

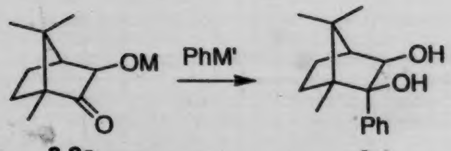
[f] Hydride reagent was added as a solution in THF.

[g] Unpurified product was used directly for the next step.

[h] Hydride reagent was added over 40 minutes.

[i] Ether used as solvent.

Following this study, we optimized the addition of the phenyl-metal reagents (Equation **3-2**, Table **3-2**), which proved to be more challenging than expected. Phenyl magnesium bromide, phenyl lithium, as well as the lesser-known phenyl cerium dichloride were examined. In order to isolate the desired diol **3.1**, an oxidative work-up was needed to break down the borinate generated after the L-Selectride® reduction. All attempts to oxidize the borinate prior to the addition of the phenyl-metal reagent were unsuccessful. The optimal results were achieved when the addition was performed on the crude reaction mixture resulting from the acidic work-up following the L-Selectride® reduction.



3.8a **3.1**

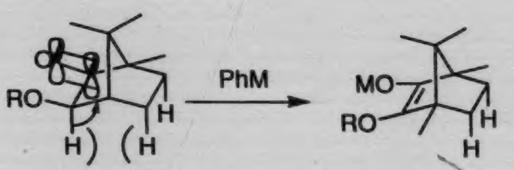
Equation 3-2

Table 3-2. Optimization of Addition of Phenyl Magnesium Bromide to **3.8a**, Route A.

entry	solvent	temp (°C)	conc (M)	equiv	yield (%)[a]
1	Ether	–40	0.4	2	-[b]
2	THF	–78	0.4	2	20
3	THF	–40	0.4	2	4
4	THF	0	0.4	2	4
5	THF	–78	0.2	1	6
6	THF	–78	0.2	2	-[b]
7	THF	–40	0.2	2	-[b]
8[c]	THF	–78	0.5	1.1	-[b]
9[d]	THF	–78	0.2	1.1	55

[a] Crystallized from petroleum ether.
[b] No product was isolated.
[c] Performed using PhLi.
[d] Performed using $PhCeCl_2$.

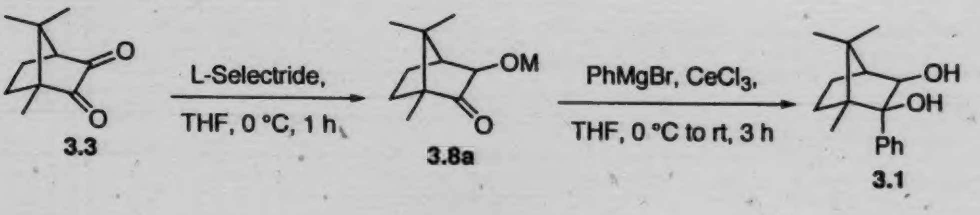
Phenyl magnesium bromide was the first reagent investigated. In most cases, none or very little product was obtained with typical yields between 0-20%. Similar results were obtained using phenyl lithium. In all of these cases, starting material was the main component of the crude reaction mixture. The phenyl cerium reagent,[10] however, proved to be the most efficient reagent and afforded the desired diol **3.1** in high yield (entry 9). This was not surprising, as cerium reagents are known to be less basic than Grignard and organolithium reagents. The lack of basicity of the cerium reagent makes it less prone to remove the rigid axial hydrogen α to the carbonyl. This side reaction could also be amplified by two factors particular to the structure of substrate **3.8a** (Equation **3-3**). The perfect alignment of the carbon-hydrogen bond with the π system of the carbonyl, as well as the release of steric interactions between the two other axial hydrogens can be involved in explaining the ease of deprotonation of this ketone. When this process happens, the starting material is regenerated upon aqueous work-up, which may explain the low conversion observed with PhMgBr and PhLi.



3.8a

Equation 3-3

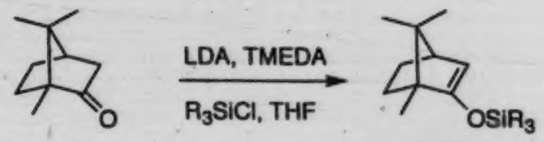
This new Route A was found to be optimal (Scheme **3-4**) when the reduction of camphorquinone (**3.3**) was performed by a slow addition of L-Selectride® at 0 °C, followed by an acidic work-up. The sequence is completed by the addition of the phenyl cerium reagent to the crude ketone **3.8a**. The ensuing oxidative work-up generates the desired diol **3.1** with an overall yield of 55% in just two steps from **3.3**. This improved sequence can be accomplished in less than 24 hours and was easily performed on more than five grams of **3.3** without any purification steps until the final crystallization of **3.1**.



Scheme 3-4

3.3 Synthesis from camphor (3.2)

The reaction sequence of Route B begins with the method reported in 1969 by House and co-workers[9] (Equation **3-4**). Thus, (*R*)-(+)-camphor (**3.2**) was treated with LDA, followed by trialkylsilylchloride and TMEDA, and afforded the desired silyl enol ethers **3.9a-c**. In the case of **3.9a** (R = Me) and **3.9b** (R = Et), the product was obtained in quantitative yield. When R = *i*-Pr, no desired product **3.9c** was observed likely due to steric bulk.



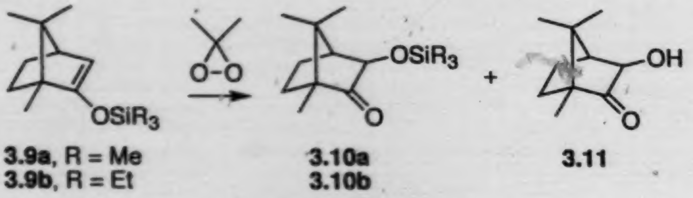
3.2

3.9a, R = Me, quant.
3.9b, R = Et, quant.
3.9c, R = *i*-Pr, 0%

Equation 3-4

The crude trimethyl or triethyl silyl enol ethers were then oxidized using a procedure of Knight and Tchabanencko (Equation **3-5**).[12] This method has certain advantages such as the *in situ* generation of DMDO, which avoids the distillation of this explosive reagent. Moreover, the reaction can be performed in an open flask. The large volume of solvent needed for the reaction (0.03 M, 120 ml for 1 g), however, makes it inefficient. This procedure also requires a large excess of the solid reagents, Oxone® and $NaHCO_3$, which makes the agitation of the heterogeneous reaction mixture difficult. A variety of reaction conditions were investigated and are reported in Table **3-3**. The first conclusion that can be drawn from the results is that the triethylsilyl enol ether **3.9b** (entry 1) is more stable to the oxidation conditions. This is shown by the 10:1 ratio of the desired product **3.10** over the deprotected alcohol **3.11** (entries 1 and 3). The oxidation of the trimethylsilyl enol ether **3.9a**, under the same conditions, gave a ratio of 3:1 (entry 2). The reaction efficiency was improved by increasing the concentration from 0.03 M to 0.25 M (1 g per 14 mL). Reducing the number of equivalents of

Oxone® and $NaHCO_3$ did not affect the outcome of the reaction (entry 5). In all cases a single diastereoisomer was observed as reported by Adam and Prechtl.[10]



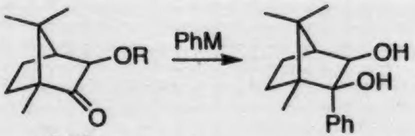
Equation 3-5

Table 3-3. Optimization of Oxidation of Silyl Enol Ethers **3.9a, b**, Route **B**.[a]

entry	conc M	equiv Oxone®	equiv $NaHCO_3$	**3.10: 3.11**[b]	yield (%)
1	0.03	5	15	10:1	71
2[c]	0.1	2.5	7.5	3:1	-[d]
3	0.1	2.5	7.5	10:1	81
4	0.25	2.5	7.5	5:1	86
5	0.25	1.5	4.5	10:1	quant.
6	0.5	2.5	7.5	5:1	86
7[e]	0.5	1.5	4.5	-[f]	-[d]

[a] All reactions were performed with **3.9b** at rt.
[b] Ratio determined by ^1H NMR of the crude reaction mixture.
[c] Done with **3.9a**.
[d] Product not isolated.
[e] Solvent was acetone:water 1:1.
[f] Reaction was incomplete.

With the desired silyloxyketone **3.10** in hand, the following step investigated was the introduction of the phenyl group to the carbonyl (Equation **3-6**). The results of a representative set of conditions tried are summarized in Table **3-4**. The use of either phenyl lithium or the phenyl Grignard reagent led to the recovery of a significant amount of starting material (entries 1-4). As previously observed, the phenyl cerium reagent was significantly better, and gave a ratio of desired product to starting material of over 10:1 (entry 6). It was also noted that the ratio of products **3.10** and **3.1** was significantly improved when the reaction was run using $PhCeCl_2$ made from PhMgBr instead of PhLi (entry 6).



3.10 **3.1**

Equation 3-6

Table 3-4. Optimization of Addition of Phenyl-Metal Reagents to **3.10**, Route B.[a]

entry	metal	solvent	**3.10: 3.1**[b]	yield (%)[c]
1	Li	THF	5:1	-[d]
2	Li	Ether	1:1	-[d]
3	Mg	THF	-[e]	-[d]
4	Mg	Ether	3:1	-[d]
5	Ce[f]	THF	3:1	-[d]
6	Ce[g]	THF	>10:1	55

[a] 1.1 equiv. of PhM, 0 °C to rt.

[b] Ratio determined by ^{1}H NMR of the crude reaction mixture.

[c] Crystallized from petroleum ether.

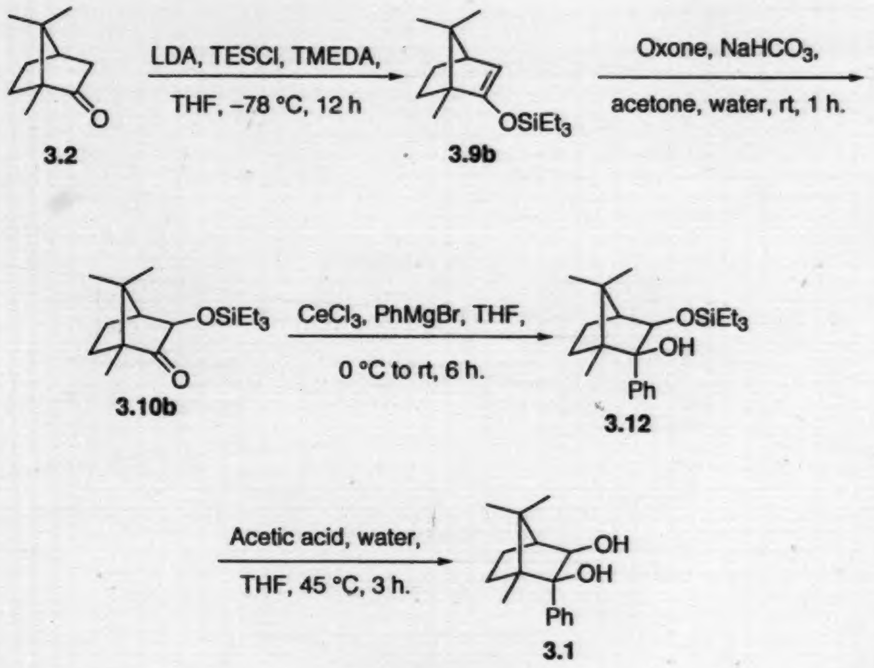
[d] Product not isolated.

[e] Mostly starting material obtained.

[f] Made using PhLi.

[g] 1.10 equiv. of PhMgBr, 1.15 equiv. of anhydrous $CeCl_3$, 0 °C to rt.

The final step requires the cleavage of the silyl ether. This can be done efficiently with TBAF, but on large scale the cost of TBAF is prohibitive. The procedure of Scheinmann and co-workers[13] was then tested for our sequence. It was found that the silyl ether could be effectively removed by heating compound **3.12** in a mixture of acetic acid, THF, and water (6.5:3.5:1) at 45 °C for three hours (Scheme 3-5). The desired diol **3.1** was obtained in a 55% yield comparable to that of the TBAF procedure. As described in Scheme **3-5**, the optimal route to diol **3.1** is through the conversion of camphor (**3.2**) to its triethylsilyl enol ether **3.9b** followed by its oxidation to the α-silyloxy ketone **3.10b** using DMDO. The sequence was completed by the addition of the phenyl cerium reagent and removal of the TES group to afford, as demonstrated on 10 grams of camphor, diol **3.1** in an overall yield of 55% without any purification steps.


3.2
LDA, TESCl, TMEDA,
THF, −78 °C, 12 h
OSiEt3
3.9b
Oxone, NaHCO3,
acetone, water, rt, 1 h.
OSiEt3
O
3.10b
CeCl3, PhMgBr, THF,
0 °C to rt, 6 h.
OSiEt3
OH
Ph
3.12
Acetic acid, water,
THF, 45 °C, 3 h.
OH
OH
Ph
3.1

Scheme 3-5

3.4 Conclusion

In summary, we have developed and optimized two new short syntheses of (–)-(1*R*,2*R*,3*R*,4*S*)-2-phenyl-1,7,7-trimethyl-2,3-bornanediol (**3.1**) that improve upon the previous literature method of preparation. Route A is performed in two steps from commercially available camphorquinone (**3.3**) with an overall yield of 55%. Route B involves four steps from the cheap, commercially available camphor (**3.2**) and also gives an overall yield of 55%. These two starting materials can be purchased in both enantiomeric forms, which allows access to either enantiomer of diol **3.1**. Both of these syntheses are efficient, practical, and were successfully performed without any purification steps on multigram scale.

3.5 Experimental

3.5.1 General

The methods described in Section 2.7.1 also apply here.

3.5.2 Route A, procedure from camphorquinone (3.3).

A solution of L-Selectride® (1 M THF, 30.1 mL, 30.1 mmol, 1.0 equiv) was added to a solution of (*R*)-(–)-camphorquinone (**3.3**) (5.0 g, 30.1 mmol, 1.0 equiv) in THF (100 mL) at 0 °C. The temperature was kept below 5 °C throughout the addition. The mixture was stirred for an additional 30 minutes. THF (100 mL) was added to a separate flame dried round bottom flask containing $CeCl_3{\cdot}7H_2O$ (13.5 g, 36.1 mmol, 1.2 equiv), which had been dried for 18 h at 140 °C under high-vacuum (<1 mmHg). The slurry was stirred at 0 °C and a solution of phenyl magnesium bromide (3 M THF, 12.0 mL, 36.0 mmol, 1.2 equiv) was added slowly. The resulting off-white suspension was stirred 30 minutes (Note: a darker solution indicates water was present). The reaction mixture was then slowly transferred using a double ended needle to the suspension using a double-ended needle. The resulting suspension was warmed-up to room temperature and left to stir for 3 h. The reaction mixture was poured slowly over a saturated aqueous solution of ammonium chloride, extracted three times with diethyl ether, dried over anhydrous magnesium sulfate, filtered, and the solvent evaporated. The resulting oil was then dissolved in a mixture of THF (50 mL), water (25 mL), 1 M aqueous sodium hydroxide (50 mL), and 30% H_2O_2 (20 mL), and the biphasic mixture was stirred at room temperature for 3 h. The mixture was extracted three times with diethyl ether; the combined ether layers were washed once with water, once with a saturated aqueous solution of $Na_2S_2O_3$, once with brine, dried over anhydrous magnesium sulfate, filtered, and the solvent was evaporated. The resulting oil was then left under vacuum (<1 mm Hg) for 6 h. The resulting product was recrystallized from petroleum ether to afford, after three crops, the desired diol **3.1** as a white crystalline powder (4.0 g, 55% from **3.3**).

3.5.3 Route B, procedure from camphor (3.2).

A solution of *n*-BuLi (1.59 M hexane, 50.0 mL, 79.5 mmol, 1.20 equiv) was added slowly to a solution of diisopropylamine (10.6 mL, 75.7 mmol, 1.15 equiv) in THF (100 mL) at –78 °C and stirred for 15 minutes. A solution of (*R*)-(+)-camphor (**3.2**) (10.0 g, 65.8 mmol, 1.00 equiv) in THF (100 mL) was added slowly to this mixture at –78 °C and stirred for 1 h. TMEDA (11.4 mL, 75.5 mmol, 1.15 equiv) and TESCl (12.1 mL, 72.3 mmol 1.10 equiv) were added and the mixture was kept at –78 °C for another hour. The reaction mixture was then warmed-up to room temperature and stirred for 12 h. The reaction mixture was poured slowly on a saturated aqueous solution of ammonium chloride and stirred for 15 minutes. The product was extracted three times with ether; the combined layers were washed once with water, once with brine, dried over anhydrous magnesium sulfate, filtered, and the solvent evaporated to afford the triethylsilyl enol ether **3.9b** as a yellow clear liquid. It was used without any further purification. Oxone® (34.6 g, 56.3 mmol, 1.50 equiv) was slowly added portion-wise (over 45 minutes) to a heterogeneous mixture of **3.9b** (10.0 g, 37.5 mmol, 1.00 equiv), and $NaHCO_3$

(14.2 g, 169 mmol, 4.50 equiv), in acetone (100 mL) and water (50 mL), in an open flask. The temperature was controlled with a water bath to keep it below 30 °C (**Caution**: DMDO is an explosive substance that is generated *in situ*; the reaction should be run in a well ventilated fume hood using proper safety precautions). The reaction was left to stir for an additional 30 min at room temperature. The reaction mixture was poured on water (500 mL) and extracted three times with ethyl acetate. The combined organic layers were washed once with a saturated aqueous solution of $Na_2S_2O_3$, once with water, once with brine, dried over anhydrous magnesium sulfate, filtered, and the solvent evaporated to afford the triethylsilyl ether ketone **3.10b** as a yellow clear liquid. It was used without any further purification. THF (100 mL) was added to a separate round bottom flask containing $CeCl_3 \cdot 7H_2O$ (15.3g, 43.4 mmol, 1.15 equiv), which was dried 18 h at 140 °C under high-vacuum (<1 mm Hg). The slurry was stirred at 0 °C and a solution of phenyl magnesium bromide (3 M THF, 13.9 mL, 41.7 mmol, 1.10 equiv) was added slowly. The resulting off-white to beige suspension was stirred for 30 minutes at 0 °C (Note: a darker solution indicates water was present). The triethylsilyl ether ketone **3.10b** (10.5 g, 37.8 mmol) in THF (20 mL) was added slowly to the slurry. The resulting suspension was stirred 30 min at 0 °C, then warmed-up to room temperature and left to stir for 6 h. The reaction mixture was poured over a saturated aqueous solution of ammonium chloride. The resulting emulsion was filtered on a pad of celite and the resulting clear solution was extracted three times with diethyl ether, dried over anhydrous magnesium sulfate, filtered, and the solvent evaporated. The resulting oil was then dissolved in a mixture of acetic acid, water, THF (65 mL, 35 mL, 10 mL) and heated for 3 h at 45 °C. Water (100 mL) and ether (200 mL) were added to the cooled reaction mixture and solid NaOH was added until the pH of the mixture was >7. The mixture was extracted three times with ether; the combined organic layers were washed once with brine, dried over anhydrous magnesium sulfate, filtered, and the solvent evaporated. The resulting oil was stirred and heated to 100 °C under high vacuum (<1 mm Hg) for 6 h to remove the leftover triethylsilanol. The resulting sticky solid was recrystallized from petroleum ether to afford, after four crops, the desired diol **3.1** as a white crystalline powder (5.2 g, 55% overall).

(–)-(1*R*,2*R*,3*R*,4*S*)-1,7,7-Trimethyl-2-phenyl-bicyclo[2.2.1]heptane-2,3-diol (3.1) is known from the literature.[5]

(1R,3R,4S)-1,7,7-Trimethyl-bicyclo[2.2.1]heptan-2-one-3-borinate (3.8a) was not isolated and was used as a one-pot procedure with the phenyl cerium addition.

(1R,4S)-1,7,7-trimethyl-2-(trimethylsilyloxy)bicyclo[2.2.1]hept-2-en (3.9a) is known from the literature[14] and was used without further purification.

(+)-(1R,4S)-1,7,7-trimethyl-2-(triethylsilyloxy)bicyclo[2.2.1]hept-2-en (3.9b)

Clear colorless liquid;

$[\alpha]^{25}_{D}$ 5.90 (c = 2.77, $CHCl_3$);

IR (neat film, cm^{-1}): 3074, 2954;

^1H NMR (300 MHz, $CDCl_3$): δ 4.58 (d, J = 3.4 Hz, 1H), 2.17 (dd, J = 3.5, 3.5 Hz, 1H), 1.87-1.80 (m, 1H), 1.53-1.45 (m, 1H), 1.24-1.20 (m, 1H), 1.17-1.01 (m, 1H), 0.97 (t, J = 7.6 Hz, 9H), 0.89 (s, 3H) 0.87 (s, 3H) 0.72 (s, 3H) 0.67 (q, J = 7.8 Hz, 6H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 128.6, 102.2, 54.7, 53.6, 49.5, 31.4, 27.4, 20.2, 19.8, 10.0, 6.7, 4.8;

Anal. Calcd for $C_{16}H_{30}OSi$: C, 72.11; H, 11.35. Found: C, 71.77; H, 11.49.

(+)-1,1,7-Trimethyl-3-(triethylsilyloxy)bicyclo[2.2.1]heptan-2-one (3.10b)

contains 10% of deprotected alcohol (11), a known compound[15].

Clear colorless liquid;

$[\alpha]^{25}_{D}$ 75.8 (c = 2.53, $CHCl_3$);

IR (CH_2Cl_2 cast, cm^{-1}): 2955, 2876, 1757;

^1H NMR (300 MHz, $CDCl_3$): δ 3.64 (s, 1H), 2.00-1.90 (m, 2H), 1.65-1.57 (m, 2H), 1.44-1.22 (m, 2H), 1.00-0.9 (m, 17H), 0.70-0.50 (m, 6H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 218.8, 78.1, 56.9, 51.1, 46.6, 29.1, 25.0, 21.1, 20.1, 9.2, 6.7, 4.9;

HRMS (EI, *m/z*) ($M-C_2H_5$) Calc'd for $C_{14}H_{25}O_2Si$: 253.1624. Found: 253.1626.

(−)-(1*R*,2*R*,3*R*,4*S*)-1,7,7-Trimethyl-2-phenyl-3-(triethylsilyloxy)-bicyclo[2.2.1]heptan-2-ol (3.12) was used as a non-purified mixture in the deprotection reaction.

3.6 References

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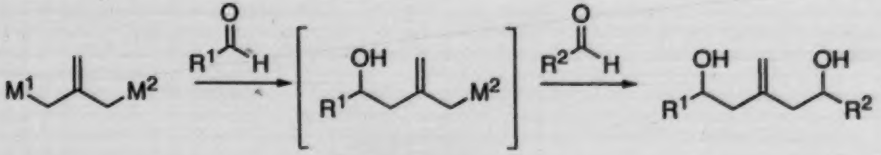
Chapter 4

Preparation and Application of Functionalized Allylboronates

4.1 Introduction

In organic synthesis, making new carbon-carbon bonds with good control is of utmost importance. When one has the ability to create more than one new bond at a time, while maintaining a high level of selectivity, it allows for efficient and quick generation of complex products. One important approach that can generate such complexity is the use of bifunctional reagents. This class of reagents includes species that will unmask a latent reactive functional group after an initial reaction. The use of such reagents gives rise to highly desirable tandem reaction approaches. There are two primary challenges that limit the development of useful bifunctional reagents, that is, their synthesis and the modulation of their reactivity. In some cases, the desired functional groups are of opposite reactivity. For example, one functional group might be a nucleophile while the other one is an electrophile. A similar situation would be when one of the two groups is base sensitive and the other one is acid sensitive. When successfully prepared, these reagents could undergo a first allylation to reveal a second allylmetal species that could in turn react with another molecule of the same or of a different aldehyde (Scheme **4-1**).


M1
M2
R1
H
O
OH
R1
M2
R2
H
O
OH
OH
R1
R2

Scheme 4-1

Two main classes of reagents of this type have been reported. The first class, exemplified by compounds **4.1** to **4.5** in Figure **4-1**, represent those with a latent second allyl metal moiety attached on the β-carbon of the first allyl unit.

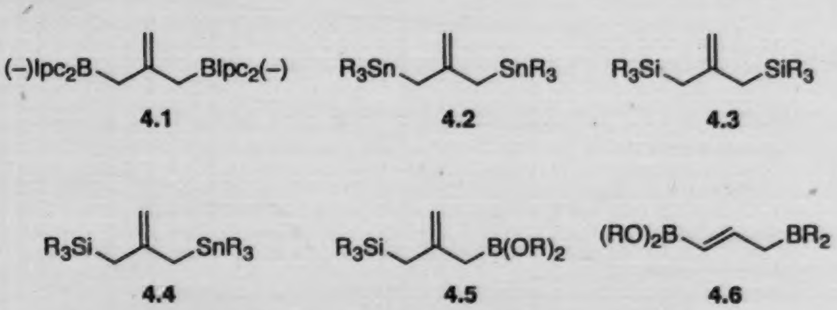
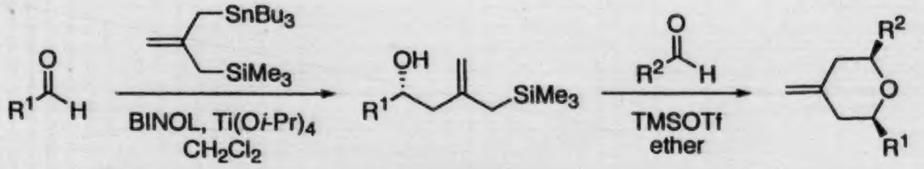

(−)Ipc2B
BIpc2(−)
4.1
R3Sn
SnR3
4.2
R3Si
SiR3
4.3
R3Si
SnR3
4.4
R3Si
B(OR)2
4.5
(RO)2B
BR2
4.6

Figure 4-1 Examples of Bifunctional Reagents

In this class, the most common reagents are those containing twice the same metal such as **4.1**, **4.2**, and **4.3**. Reagents such as **4.1** have been shown to undergo double aldehyde allylation.[1,2] Unfortunately, due to the identical nature of both boron species, it was impossible to efficiently modulate their reactivity to perform two sequential allylations with two different aldehydes. All attempts led to poor or no control at all. In the case of reagents containing two tin centers, they have been used under radical conditions.[3] They have also been used, with limited success, in double allylation sequences.[4] On the other hand, reagents containing two silicon groups have been used as a "linchpin" in the bidirectional synthesis of polyols.[5] The main advantage of these reagents is the possibility of using them with acetals as electrophiles in presence of a Lewis acid.[6]

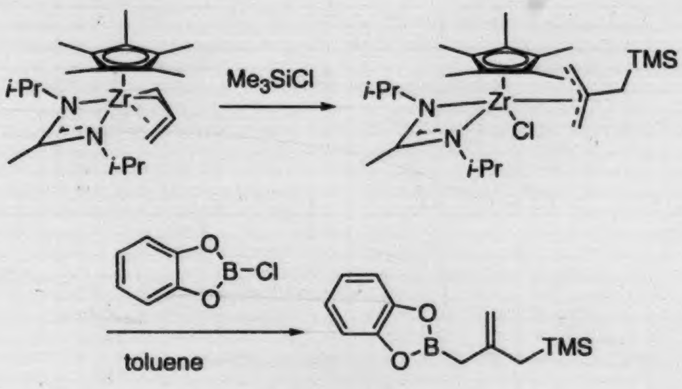
Many applications have been found for the mixed silicon-tin species. Of important significance is the work of Keck and co-workers,[7] which utilized the allyl-tin species with the titanium tetraisopropoxide-Binol catalyzed enantioselective aldehyde allylation methodology. The resulting allylsilane was then used to performe a Prins reaction (Scheme **4-2**). This strategy was used in the syntheses of (+)-dactylolide and analogues of bryostatins.[8,9]


SnBu3
SiMe3
BINOL, Ti(Oi-Pr)4
CH2Cl2
R1
H
O
OH
SiMe3
R2
H
TMSOTf
ether
R2
R1
O

Scheme 4-2

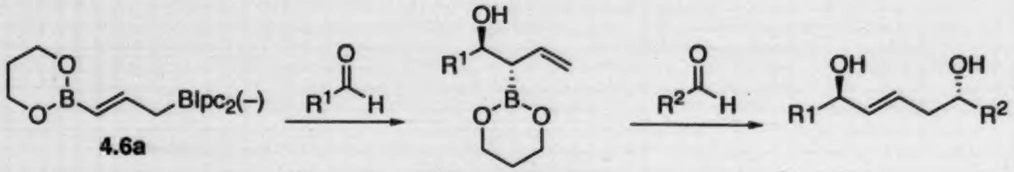
One of these mixed silyl-tin reagents has also been used by Clive and co-workers.[10] In this case, the allylstannane first underwent a radical reaction to generate the latent allylsilane, which was then reacted with a pendent carbonyl group. A large number of variations based on these two examples have been reported with these reagents.[3,4,11]

Just recently a procedure to generate the type **4.5** reagent has been published (Scheme **4-3**),[12] however, no application of that reagent has been reported yet.

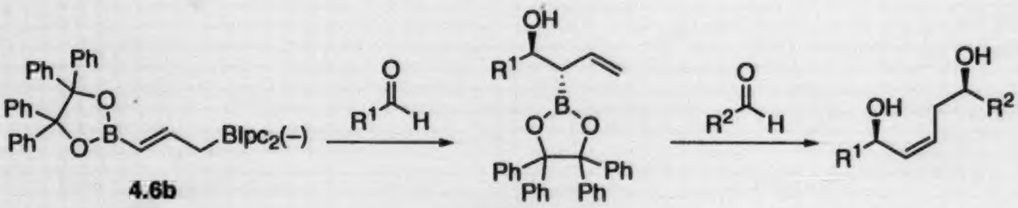

i-Pr
N
Zr
N
i-Pr
Me3SiCl
i-Pr
N
Zr
Cl
N
i-Pr
TMS
O
B–Cl
O
toluene
O
B
O
TMS

Scheme 4-3

One other class of interesting bis-allylating species includes reagents that contain γ-metal substituents. Of particular interest are the ones developed by Roush,[13] such as **4.6** in Figure **4-1**, where both metals are boron. In this case, once the more reactive allylborane has reacted with the first aldehyde, an allylboronate is unveiled. By changing the nature of the boronic ester from 1,3-ethylene diol **4.6a** (Scheme **4-4**) to the tetraphenylethylenediol group **4.6b**, it is possible to control the selectivity of the second addition (Scheme **4-5**). These two reagents have been applied towards the synthesis of amphidinol 3. [14,15]



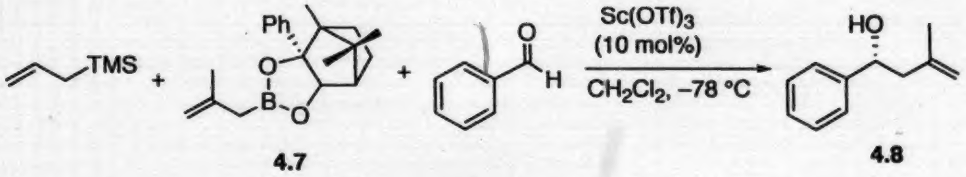
Scheme 4-4



Scheme 4-5

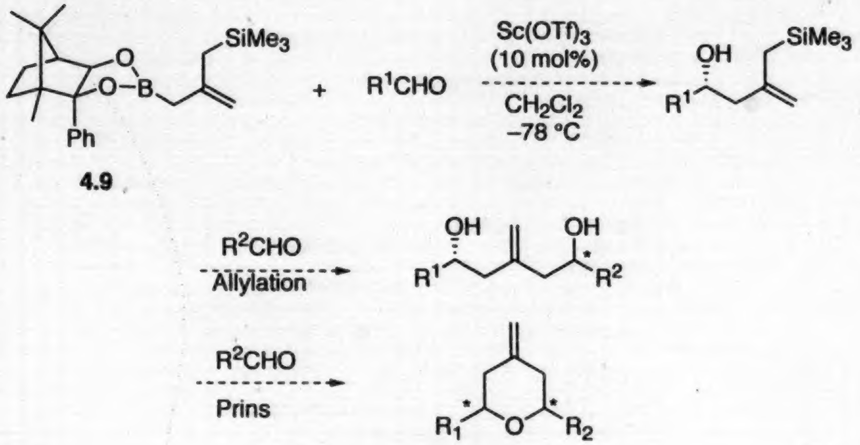
4.2 Design of a double allylation reagent

The success of our enantioselective catalytic allylboration reaction has prompted us to look at broadening its scope of applications. The success of the methallylation variant encouraged us to look at β-substituted bifunctionalized reagents. Two factors were to be investigated. The first one to be addressed was the selectivity issue: in the presence of both an allylsilane and an allylboronate unit, which one would react first under the catalytic manifold? To this end, a simple competitive experiment was performed. One equivalent of allyltrimethylsilane and one equivalent of boronate **4.7** were reacted with one equivalent of benzaldehyde under the typical catalytic conditions (Equation **4-1**). This experiment showed by proton NMR spectroscopy the presence of the allylboration product **4.8** as sole product, no product of allylsilation was observed. This result indicated that activation of the boronate towards allylboration is more efficient than aldehyde activation towards allylsilation. One point that should be noted is that the model boronate used was a methallyl reagent, hence, was slightly more reactive than the unsubstituted allyl species due to the synergistic electron donating nature of the β-methyl group.


TMS
+
Ph
O
B
O
+
O
H
Sc(OTf)3
(10 mol%)
CH2Cl2, –78 °C
HO
4.7
4.8

Equation 4-1

The second factor that needed to be investigated was the level of diastereoselectivity of the second reaction, either an allylsilation or a Prins reaction (Scheme **4-6**). In the meantime, an efficient synthesis for reagents of the type **4.9** had to be found.


SiMe3
O
O–B
Ph
4.9
+
R1CHO
Sc(OTf)3
(10 mol%)
CH2Cl2
–78 °C
OH
SiMe3
R1
R2CHO
Allylation
OH
OH
R1
R2
R2CHO
Prins
R1
O
R2

Scheme 4-6

4.2.1 Attempted synthesis of functionalized reagents

In our approaches towards reagents **4.9**, a few general strategies were identified (Figure **4-2**). The first route to be ruled out was the use of intermediate **4.10**. Because a dianion was involved in this strategy, it would be difficult to control the selectivity of the reaction. The use of dianions would lead to a statistical mixture of the desired product, plus a mixture of species containing the same metal twice, either two boron atoms or two silyl groups.

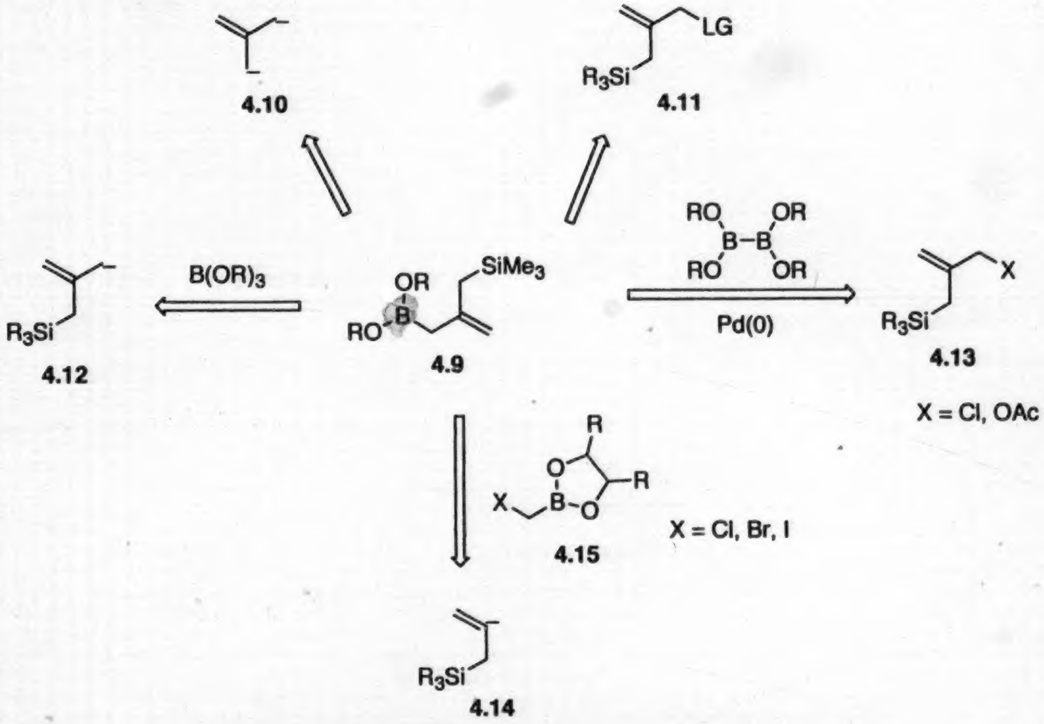
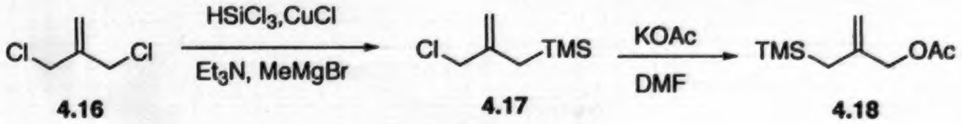

4.10
LG
R3Si
4.11
B(OR)3
OR
RO
B
SiMe3
4.9
RO OR
B–B
RO OR
Pd(0)
X
R3Si
4.13
X = Cl, OAc
R3Si
4.12
R
O
R
X
B
O
4.15
X = Cl, Br, I
R3Si
4.14

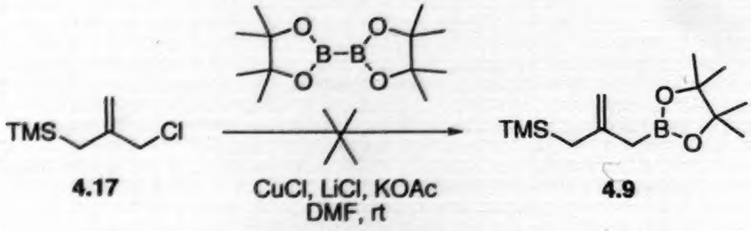
Figure 4-2 Approaches Towards Allylboronate **4.9**

The next approaches to be ruled out were those involving nucleophilic displacement of an allylic leaving group such as **4.11**. The literature reports very few examples of boron acting as a nucleophile. The most common situation is in the case of the Hosomi-Miyaura reaction. In this case, boron is a copper based nucleophile, and the electrophile is, in most cases, a Michael acceptor.[16-18] There is only one report where a leaving group is used to perform an S_N2' reaction but this is done in the presence of a strong electron-withdrawing group at the β-position.[19] Nevertheless, this approach was attempted. The necessary precursors **4.17** and **4.18** were prepared from **4.16** according to known procedures in reasonable yields of 50% and 33% respectively (Scheme **4-6**).[20]

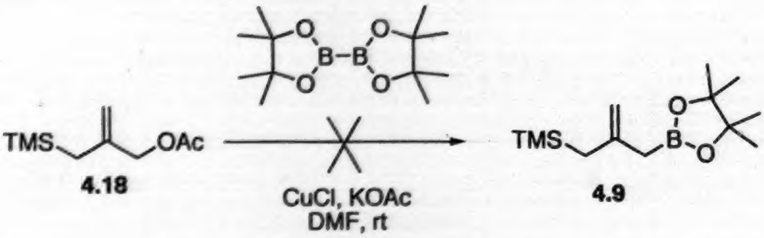


Scheme 4-7

Unfortunately, when applied to substrates **4.17** and **4.18** (Equations **4-2** and **4-3**), the Hosomi-Miyaura conditions led to the recovery of the starting material in both cases.

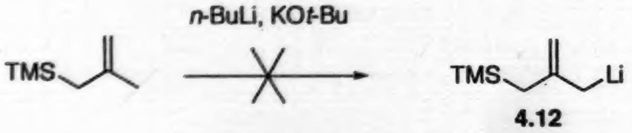

TMS
Cl
4.17
CuCl, LiCl, KOAc
DMF, rt
TMS
4.9
O
B
O

Equation 4-2


TMS
OAc
4.18
CuCl, KOAc
DMF, rt
TMS
4.9
O
B
O

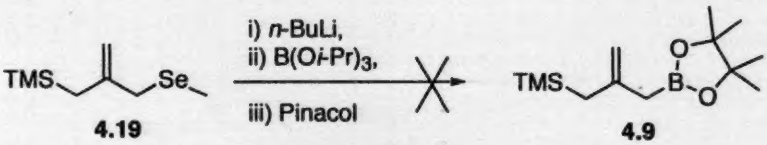
Equation 4-3

The approaches proceeding through carbanionic intermediate **4.12** (Figure **4-2**) were investigated under a range of different conditions. Methallyltrimethylsilane was reacted under Schlosser's base conditions but no deprotonation was observed and the volatile starting material was recovered (Equation **4-4**).

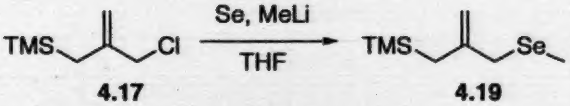

n-BuLi, KO*t*-Bu
TMS
TMS
Li
4.12

Equation 4-4

The possibility of forming the desired anion **4.12** through selenide **4.19** was also investigated (Equation **4-5**). The required dialkylselenide **4.19** was prepared from **4.17** in good yield (90%) according to a literature procedure (Equation **4-6**).[21] Unfortunately, when the anion was reacted with triisopropylborate at –78 °C followed by treatment with pinacol, no desired product could be isolated. From the crude ^{1}H NMR spectrum, no starting material could be observed but no product was present either. Two possibilities can be put forward. Either the anion formed was protonated in the aqueous work-up step providing the volatile methallyltrimethylsilane, or the desired product was formed and decomposed at higher temperature (room temperature) or even during the work-up process.

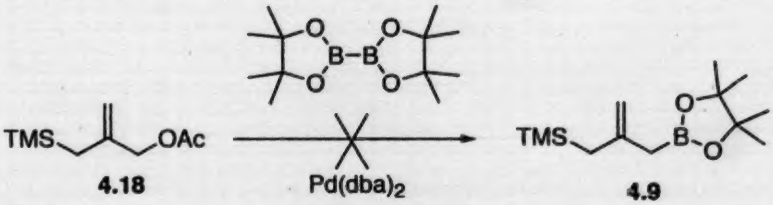


Equation 4-5



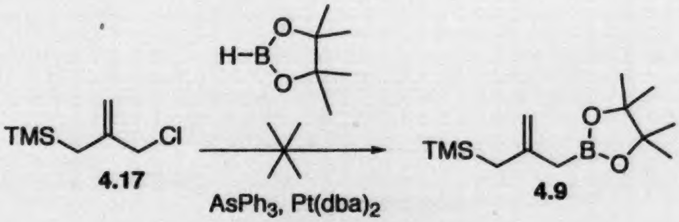
Equation 4-6

The following strategies using metal catalyzed coupling reactions with the appropriate precursor (i.e. **4.13** Figure **4.2**), were carried out under a large number of different conditions. Treating allylic acetate **4.18** under standard palladium coupling conditions using $Pd_2(dba)_3$ and bis-(pinacolato)diboron, at 50 °C in DMSO,[22] only led to the recovery of starting material **4.18** (Equation **4-7**). This observation indicated that substrate **4.18** was inert to the oxidative insertion step under these conditions.



Equation 4-7

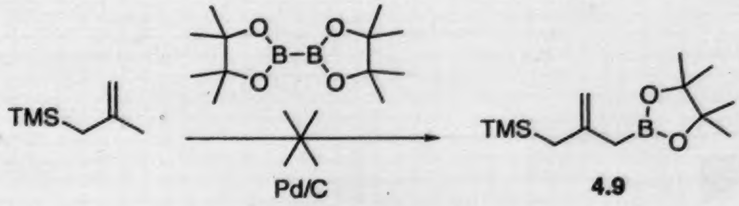
Attempts at functionalizing allylic chloride **4.17** using $Pt(dba)_2$, triphenylarsine and pinacol borane,[23] also provided starting material even after 48 h at 50 °C in toluene (Equation **4-8**).



Equation 4-8

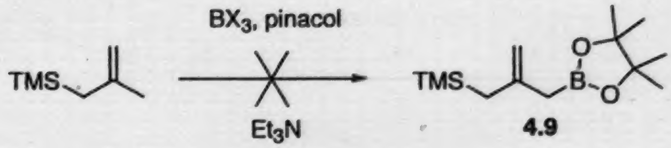
Likewise, direct functionalization of methallyltrimethylsilane using palladium on charcoal and bis-(pinacolato)diboron at 100-150 °C in a sealed tube for up to

5 days showed no reaction and no decomposition of the starting material (Equation **4-9**).[24]



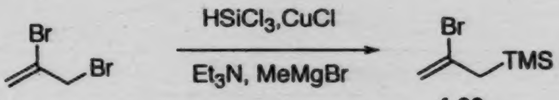
Equation 4-9

Direct functionalization of methallyltrimethylsilane, through a possible ene type reaction using a boron trihalide (either BBr_3 or BCl_3) and triethylamine (Equation **4-10**), led to decomposition yielding complex inseparable mixtures. In this case, the generation of the chloride or bromide anion may interfere with the allylsilane species present.



Equation 4-10

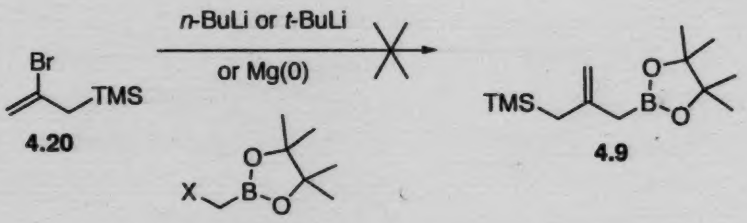
In the course of many projects in our group, halide **4.15** (c.f. Figure **4-12**) was used to react with electrophiles to generate allylboronate species.[25] In the context of our target, it could be reacted with a nucleophile of analogous structure to that of **4.14** (Figure **4-2**). To access intermediates of that type, a common intermediate **4.20** was required. It was prepared based on a literature procedure in 65% yield (Equation **4-11**).[26]



4.20

Equation 4-11

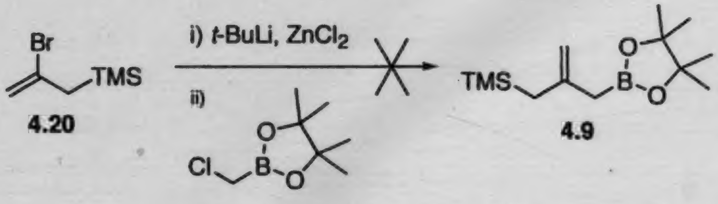
With the β-bromo allylsilane in hand, we tried to perform the alkylation using the chloro, bromo or iodo electrophile **4.15** (Equation **4-12**). The anion was generated either through lithium halogen exchange or through the formation of a Grignard reagent (Equation **4-12**).



4.20 **4.15** **4.9**

Equation 4-12

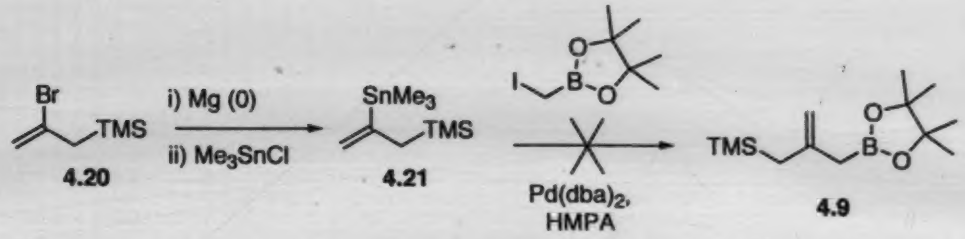
None of these approaches gave any traces of the desired product. Since in most of these cases the starting material disappeared, the metallation is probably not the problematic step. It was impossible to isolate any significant side product out of these reactions. Any product coming from the protonation of the anion would produce a volatile allylsilane that would be lost during operations of solvent evaporation. On the other hand, the desired product might be formed and decomposed upon warming up the reaction or during the work-up. To rule out this possibility, a one-pot procedure was attempted where the alkylation was carried out at –78 °C and either kept at that temperature or warmed-up to higher temperatures (–40 °C and 0 °C) followed by the addition of benzaldehyde at –78 °C. The reaction was then left to react while allowing the vessel to slowly warm up to room temperature. None of these attempts afforded any product relating to an allylboration reaction or to any reaction sequence (allylboration/allylsilation or allylboration/Prins reaction). In the hope of changing the nature of the nucleophile, another attempt was made to transmetallate the lithiated intermediate to zinc. This nucleophile also did not lead to any desired product (Equation **4-13**).[27]



Equation 4-13

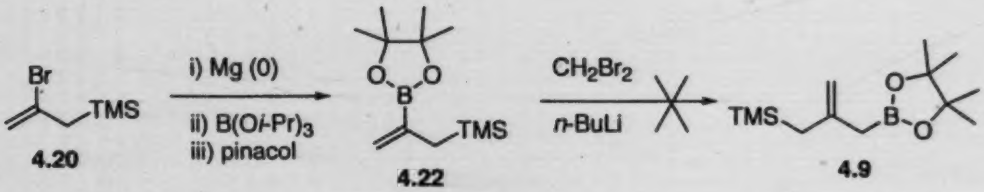
Based on a procedure reported by Falck and co-workers,[28] we tried to couple the known intermediate **4.21**[29] with iodomethylpinacolboronate

(Scheme **4-8**) under typical Stille coupling conditions ($Pd_2(dba)_3$ in HMPA). Even after 36 h at 60 °C, only starting material was recovered.


Br
TMS
4.20
i) Mg (0)
ii) Me_3SnCl
$SnMe_3$
TMS
4.21
I
B
O
$Pd(dba)_2$,
HMPA
TMS
4.9

Scheme 4-8

Again using bromide **4.20** as starting material, we prepared boronate **4.22**. All attempts at performing the Matteson homologation[30] failed and only starting material was recovered (Scheme **4-9**).


Br
TMS
4.20
i) Mg (0)
ii) $B(Oi\text{-}Pr)_3$
iii) pinacol
O
B
TMS
4.22
CH_2Br_2
n-BuLi
TMS
4.9

Scheme 4-9

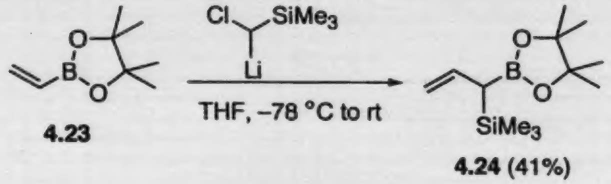
4.3 α-Substituted allylboronates

As mentioned in the introduction and depicted in Figure **1-8** and Scheme **1-3**, enantioenriched α-substituted allylboronates provide excellent transfer of chirality. At the same time, they may also allow for the introduction of new functional groups, thus generating allylation products possessing more complexity. The main limitation of these reagents is their preparation, and when it is possible to access them, the control of the *E/Z* selectivity in the formation of the disubstituted double bond is often challenging. With the development of the new catalytic manifold operative at low temperature, the effect of catalysis on the selectivity of the addition of α-substituted allylboronates was a worthwhile investigation. Furthermore, it could also reveal important information on the mechanism of the Lewis and Brønsted acid-catalyzed allylboration reactions.

4.3.1 Synthesis of α-substituted allylboronates

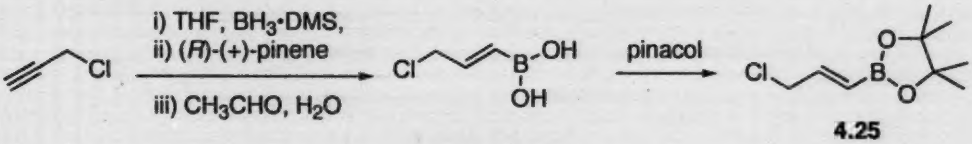
To allow for a quick and efficient study of the reactivity and selectivity of the Lewis acid-catalyzed allylboration reaction of α-substituted allylboronates with aldehydes, pinacol allylic boronates were used due to their ease of handling and their stability to chromatographic conditions and moisture. It also allowed for optimization of the *Z/E* ratio of addition products.[31] Thus, α-trimethylsilyl, and α-dimethylphenylsilyl reagents **4.24**, **4.26** and **4.28** were prepared using known methods as shown in Equations **4-14** to **4-16**. Accordingly, the α-trimethylsilyl reagent **4.24** was synthesized using a Matteson homologation on vinylboronate

4.23 (Equation **4-14**).[30] Any attempts at preparing the Hoffmann diol analogue were unsuccessful due to steric hindrance from the bulky boronic ester.


Cl
SiMe3
Li
THF, −78 °C to rt
O
B
O
4.23
SiMe3
4.24 (41%)

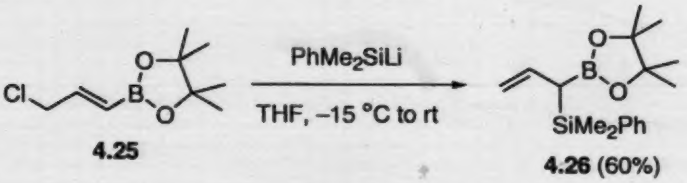
Equation 4-14

In order to access compounds **4.26** and **4.28**, alkenyl pinacol boronate **4.25** was prepared according to the literature[32] as described in Scheme **4-10**.


Cl
i) THF, BH3•DMS,
ii) (R)-(+)-pinene
iii) CH3CHO, H2O
Cl
B
OH
OH
pinacol
Cl
O
B
O
4.25

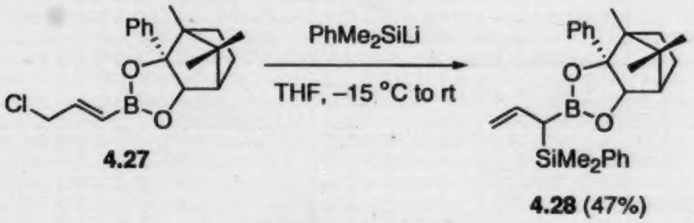
Scheme 4-10

Reagent **4.26** was synthesized through a selective S_N2' addition (or vinylogous Matteson rearrangement) of dimethylphenylsilyl lithium[33] to the known 3-chloropropenylboronate **4.25**[32] (Equation **4-15**).[34] In this case, the selectivity of the S_N2' addition over the S_N2 addition was determined in the crude ^{1}H NMR spectrum and was consistently over 8:1 in favour of the S_N2' addition product.


Cl
O
B
O
PhMe$_2$SiLi
THF, –15 °C to rt
O
B
O
SiMe$_2$Ph
4.25
4.26 (60%)

Equation 4-15

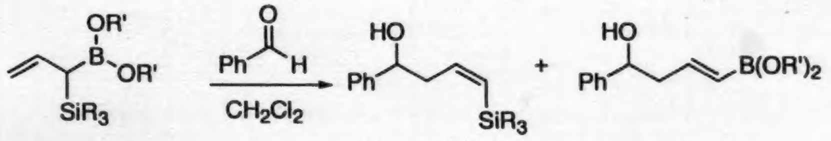
Reagent **4.28** was also synthesized using the selective S_N2' addition on **4.27**, using dimethylphenylsilyl lithium[33] (Equation **4-16**). Even if the yield of this transformation is still low (47%), the selectivity remains good. The selectivity of the S_N2' addition over the S_N2 addition was determined in the crude ^1H NMR spectrum and was again over 8:1 in favour of the S_N2' addition product. The modest yields for the preparation of these reagents have not been optimized. We preferred to first test their reactivity; these studies are discussed in the next section. For the same reasons, the stereochemistry at the α-carbon of boronate reagent **4.28** was not assigned.


Ph
O
B
O
Cl
PhMe$_2$SiLi
THF, –15 °C to rt
Ph
O
B
O
SiMe$_2$Ph
4.27
4.28 (47%)

Equation 4-16

4.3.2 Applications

In the quest to gain further insight into the reaction mechanism of the Lewis and Brønsted acid-catalyzed allylboration of aldehydes, the newly prepared α-silyl substituted reagents **4.24**, **4.26,** and **4.28** were submitted to the catalytic conditions. Indeed, as observed by Hiyama and co-workers, [35] addition of these reagents to aldehydes can lead either to alkenylsilane products **4.29a/4.29b** via thermal allylboration, or to the alkenylboronate **4.30a/4.30b** via $TiCl_4$-catalyzed allylsilation. The nature of products observed would reveal information on the preferred mode of activation by the catalyst, i.e. aldehyde activation in the allylsilation versus boronate activation in the allylboration (Equation **4-8**). The modest yields of products observed in these allylation reactions is probably a reflection of the steric strain created by the presence of the bulky α-silyl group (Table **4-1**). However, aside from products, starting materials were recovered with very little degradation. With all three reagents **4.24**, **4.26**, and **4.28** the thermal reaction conditions promoted the expected allylboration pathway to give the *Z*-alkenylsilanes **4.29a** and **4.29b** as major products (entries 1, 4 and 7).



4.29a, b

4.30a, b

4.24 (Ra = $SiMe_3$,
Ra' = CMe_2CMe_2)
4.26 (Rb = $SiMe_2Ph$,
Ra' = CMe_2CMe_2)
4.28 (Rb = $SiMe_2Ph$,
Rb' = (R)-Hoffmann)

Equation 4-17

Table 4-1. Allylboration of α-Silyl Allylboronates with Benzaldehyde.[a]

entry	boronate	catalyst	T (°C)	Time (h)	product	*E*/*Z*	Yield (%)[b]
1	**4.24**	none	0	15	**4.29a**	1:6.7	46
2	**4.24**	$Sc(OTf)_3$	–78	40	**4.30a**	4:1	40
3	**4.24**	TfOH	–78	40	**4.30a**	3:1	43
4	**4.26**	none	0	15	**4.29b**	1:6.2	22
5	**4.26**	$Sc(OTf)_3$	–78	40	**4.30a**	4:1	21
6	**4.26**	TfOH	–78	40	**4.30a**	4:1	26
7	**4.28**	none	0	15	**4.29b**	-[c]	<45
8	**4.28**	$Sc(OTf)_3$	–78	40	**4.29b**	-[c]	17
9	**4.28**	TfOH	–78	40	**4.29b/4.30b**	-[c]	10/25

[a] Typical reaction scale: approx. 0.3 mmol, 0.2 M in dichloromethane.
[b] Unoptimized yields of pure products isolated after flash chromatography.
[c] Only *Z* product observed.

The predominance of the *Z*-isomers of **4.29/4.30** whne the allylboration process operates, can be explained by the large size of the silyl group, which would aggravate the non-bonded interactions with the pinacolate group in the transition state (Figure **4-3**).

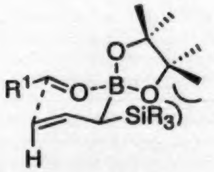
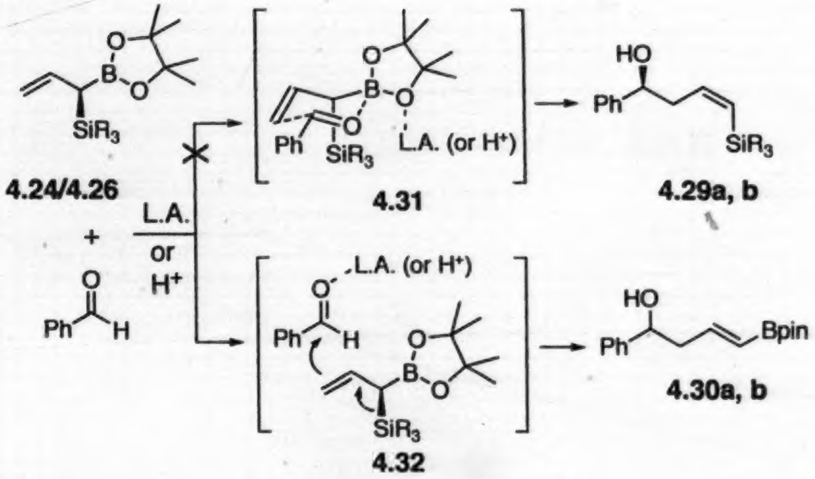


Figure 4-3 Non-Bonding Interactions in the Addition of α-Substituted Allylboronates

To our initial surprise, both the Sc(OTf)$_3$ and TfOH-catalyzed reactions with boronates **4.24** and **4.26** provided the *E*-alkenylboronate **4.30** as the major product of what appeared to be acid-catalyzed allylsilations (entries 2, 3, 5, 6). No allylboration products were observed. This interesting switch of chemoselectivity can be explained by a preference for the aldehyde activation mode (i.e., transition state assembly **4.32**) over the electrophilic boronate activation mode (**4.31**) expected in the absence of an α-silyl substituent (Scheme **4-11**).



Scheme 4-11

The case of boronate **4.28** is worth discussing separately. As mentioned above (entry 7 Table **4-1**), the thermal allylboration reaction provided the desired alkenylsilane **4.29b** in a yield of 45% and an enantioselectivity of 42%. After purification by flash chromatography, the product was contaminated with 10% of the chiral diol. When the reaction is performed under Lewis acid-catalysis, the allylboration product was obtained in low yield (17%) and low enantioselectivity (69% ee). Although this result was an improvement in selectivity compared to the thermal reaction, it was still at an impractical level. The low yield obtained from this reaction also limited the usefulness of this reaction. In this case, the remainder was starting material. When the same reaction was run under the triflic acid conditions, a mixture of products was obtained. Alkenylsilane **4.29b** and alkenylboronate **4.30b** were obtained in 10% and 25% yields respectively. The low yield, the improved level of stereoselectivity (i.e. *E*/*Z* ratio) and the difference in chemoselectivity, can be explained by the increased steric strain between the bulky chiral diol and the dimethylphenylsilyl group compared to the case where a less bulky pinacolate unit is used.

4.4 Conclusion

In conclusion, although they are potentially very useful reagents, bifunctional allylboration reagents have proven to be of unexpected complexity to prepare. In particular, the preparation of the β-substituted allylboronate **4.9** (Section **4.2** and **4.3**) was troublesome enough that we were unable to prepare it. Thus, it was impossible to address our initial hypothesis that these reagents could be used in tandem reactions with aldehydes either through allylsilation or the Prins reaction. Due to their huge potential, an eye should be kept open for new methodologies that could allow access to this class of reagents. In the case of the α-silyl substituted allylboronates, some interesting conclusions can be drawn. Firstly, in all the cases of α-silyl substituted allylboronates, the reagents are very hindered. This is reflected by the low yields and long reaction times observed in the addition of these reagents to aldehydes. Secondly, under Lewis or Brønsted acid catalysis, α-silyl pinacol allylic boronates react under the allylsilation manifold. Thirdly, when the camphor-derived allylboronate is used without catalysis, the enantioselectivity is poor and is only slightly improved under $Sc(OTf)_3$ catalysis

(42 to 60% ee). Most interesting is the fact that when scandium trifluoromethane sulfonate is used as catalyst, the boronate species seems to be more reactive than the allylsilane. When the smaller, more reactive, Brønsted acid triflic acid is used, a mixture of products is obtained (alkenylsilane **4.29b** and alkenylboronate **4.30b**).

4.5 Experimental

4.5.1 General

The methods described in Section 2.7.1 also apply here.

4.5.2 Experimental procedures

2-(Chloromethyl)-3-(trimethylsilyl)propene (4.17)

This compound is known and was prepared according to the literature procedure.[20] Spectral data for **4.17** can be found in reference 20.

2-(Acetoxymethyl)-3-(trimethylsilyl)propene (4.18)

This compound is known and was prepared according to the literature procedure.[20] Spectral data for **4.18** can be found in reference 20.

2-((Trimethylsilyl)methyl)-3-(methylseleno)prop-1-ene (4.19)

This compound is known and was prepared according to the literature procedure.[21] Spectral data for **4.19** can be found in reference 21.

2-Bromo-3-(trimethylsilyl)-1-propene (4.20)

This compound is known and was prepared according procedure B in the literature.[26] Spectral data for **4.20** can be found in reference 26.

2-(trimethylstannyl)-3-(trimethylsilyl)-1-propene (4.21)

This compound is known[37] and was prepared according to the literature procedure. [29] Spectral data for **4.21** can be found in reference 37.

Pinacol 3-(trimethylsilyl)-1-propene-2-boronate (4.22)

In a flame dried flask under inert atmosphere, magnesium turnings (53 mg, 2.2 mmol, 1.1 equiv) were charged, suspended in THF (1.5 mL) and stirred at room temperature. Bromide **4.20** (384 mg, 2.0 mmol, 1.0 equiv in 0.5 mL of THF) was added dropwise and the mixture was stirred at reflux for 1 h. The reaction mixture was then cooled to room temperature and triisopropylborate (451 mg (553 μL), 2.4 mmol, 2.2 equiv) was added. The reaction mixture was stirred at room temperature for 4 h. The reaction was then poured over a mixture of saturated aqueous ammonium chloride (20 mL), ether (20 mL) and pinacol (213 mg 1.80 mmol, 0.8 equiv). The phases were then separated, the aqueous phase was extracted three times using ether. The combined organic phases were washed once with brine, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. The crude mixture was then purified by bulb-to-bulb distillation (oven temperature: 225 °C) and afforded 154 mg (40% yield) of boronate **4.22** as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.66 (d, $J = 3.6$ Hz, 1H),5.43-5.38 (m, 1H),1.67 (br s, 2H), 1.26 (s, 12H), –0.01 (s, 9H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 126.8, 83.4, 25.4, 24.9, 24.6, –1.8.

Pinacol 3-(trimethylsilyl)-1-propene-3-boronate (4.24)

This compound is known and was prepared according to the literature procedure.[30a] Spectral data for **4.24** can be found in reference 30a.

Pinacol (*E*)-3-Chloroprop-1-enylboronate (4.25)

In a dry round bottom flask, (*E*)-3-chloroprop-1-enylboronic acid[32] (120 mg, 1.0 mmol, 1 equiv) and pinacol (118 mg, 1.0 mmol, 1 equiv) the mixture was dissolved in 5 mL of CH_2Cl_2 and evaporated in vacuo, the dissolution-evaporation was repeated three times. The crude product **4.25** was used without any purification. Spectral data for **4.25**[34] can be found in reference 34.

Pinacol 3-(dimethylphenylsilyl)-1-propene-3-boronate (4.26)

This compound is known[35] and was prepared according to the following procedure.

In a flame dried flask under inert atmosphere, crude alkenylboronic ester **4.25** (202 mg, 1.0 mmol, 1.0 equiv) was charged, diluted with THF (2 mL) and cooled to –15 °C in an ethylene glycol, dry ice bath. A freshly prepared solution of dimethylphenylsilyl lithium 1.0 M in THF (2.0 mL, 2.0 mmol, 2.0 equiv)[33] was added dropwise and the mixture was stirred for 30 minutes at –15 °C. The reaction mixture was then warmed to room temperature and stirred overnight. The reaction mixture was quenched with an aqueous solution of saturated ammonium chloride and stirred at room temperature. The phases were then separated, the aqueous phase was extracted three times using dichloromethane. The combined organic phases were washed once with brine, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. The crude mixture was then purified by flash chromatography on silica gel using 95% hexanes : 5% ethyl acetate as eluent and afforded 180 mg (60% yield) of boronic ester **4.26** as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60-7.48 (m, 2H), 7.38-7.28 (m, 3 H), 5.85 (ddd, *J* = 16.8, 10.5, 10.5 Hz, 1H), 4.78 (dd, *J* = 10.5, 2.2 Hz,1H), 4.74 (ddd, *J* = 16.8, 2.2, 0.6 Hz, 1H), 1.79 (d, *J* = 10.5 Hz, 1 H), 1.16 (s, 12H), 0.34 (s, 6H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.0, 135.3, 133.9, 128.8, 127.4, 112.2, 82.8, 24.8, –3.2.

(1*R*,2*S*,3*R*,4*S*)-2,3-O-[(*E*)-3-Chloroprop-1-enylboryl]-2-phenyl-1,7,7-trimethylbornanediol (4.27)

This compound is new and was prepared according to the same procedure as compound **4.25**.This compound was used crude without any purification.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46-7.42 (m, 2H), 7.37-7.27 (m, 3H) 6.63 (ddd, *J* = 17.6, 6.0, 6.0 Hz, 1H), 5.75 (ddd, *J* = 17.7, 1.5, 1.5 Hz, 1H), 4.78 (s, 1H), 4.09 (dd, *J* = 6.1, 1.7 Hz, 2H), 2.17 (d, *J* = 5.5 Hz, 1H), 1.89-1.79(m, 1H), 1.54 (s, 3H), 1.26-1.14 (m, 2H), 1.08-1.00 (m, 1H), 0.98 (s, 3H), 0.94 (s, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.9, 141.7, 127.5, 127.4, 126.7, 96.0, 88.8, 52.1, 50.5, 48.9, 46.1, 29.7, 24.8, 23.7, 21.1, 9.4.

3-(dimethylphenylsilyl)-1-propene-3-[(1*R*,2*S*,3*R*,4*S*)-2,3-O-2-phenyl-1,7,7-trimethylbornanediol]boronate (4.28)

In a flame dried flask under inert atmosphere, crude alkenylboronic ester **4.27** (330 mg, 1.0 mmol, 1.0 equiv) was charged, diluted with THF (2 mL) and cooled to −15 °C in an ethylene glycol, dry ice bath. A freshly prepared solution of dimethylphenylsilyl lithium 1.0 M in THF (2.0 mL, 2.0 mmol, 2.0 equiv) [33] was added dropwise and the mixture was stirred for 30 minutes at −15 °C. The reaction mixture was then warmed to room temperature and stirred overnight. The reaction mixture was quenched with an aqueous solution of saturated ammonium chloride and stirred at room temperature. The phases were then separated, the aqueous phase was extracted three times using dichloromethane. The combined organic phases were washed once with brine, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. The crude mixture was then purified by flash chromatography on silica gel using 95%

hexanes : 5% ethyl acetate as eluent and afforded 200 mg (47% yield) of boronic ester **4.28** as a colorless oil.

IR (CH_2Cl_2 cast film, cm^{-1}) 3068, 3050, 2999, 2956,1640, 1621;

^1H NMR ($CDCl_3$, 300 MHz) δ 7.59-7.05, (m, 10H), 5.88 (ddd, *J* = 16.8,10.4,10.4 Hz, 1H), 4.82-4.72 (m, 2H), 4.56 (s, 1H), 2.07 (d, *J* = 5.1 Hz, 1H), 1.86-1.70 (m, 2H), 1.23-1.09 (m, 2H), 1.16 (s, 3H), 1.04-0.96 (m, 1H), 0.95 (s, 3H), 0.90 (s, 3H), 0.19 (s, 3H), 0.14 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 141.8, 137,7, 135.2, 134.0, 133.8, 133.7, 133.6, 133.3, 128.7, 128.4, 127.7, 127.3, 127.2, 112.1, 95.7, 88.1, 51.9, 50.3, 48.8, 29.5, 24.7, 23.5, 21.0, 9.4, –3.6, –3.9;

HRMS (ESI) m/z calcd for $C_{27}H_{35}BO_2SiNa$: 453.2392. found: 453.2392.

1-Phenyl-4-trimethylsilyl-but-3-en-1-ol (4.29a)

This compounds is known.[30] The reaction was performed according to the literature procedure.[30] Spectral data for **4.29a** can be found in reference 30.

4-(Dimethylphenylsilyl)-1-Phenyl-but-3-en-1-ol (4.29b)

This compound is known[35] and was prepared according to the literature procedure.[30] Spectral data for **4.29b** can be found in reference 35.

^{1}H NMR (300 MHz, CDCl$_3$): δ 7.58-7.48 (m, 2H), 7.42-7.16 (m, 8H), 6.46 (dt, *J* = 13.9, 7.4 Hz, 1H), 5.85 (dt, *J* = 13.9, 1.3 Hz, 1H), 4.64 (dd, *J* = 7.4, 5.6 Hz, 1 H), 2.65-2.35 (m, 2H), 1.71 (br s, 1H), 0.38 (s, 6H);

^{13}C NMR (125 MHz, CDCl$_3$): δ 145.6, 143.8, 139.3, 133.7, 130.6, 128.9, 128.3, 127.8, 127.4, 125.7, 73.6, 43.0, 1.0, –1.0;

HPLC: Chiralcel OD-RH, 60% *i*-PrOH/H$_2$O, 0.4 mL/min., UV detection at 210 nm, major peak at 61.1 min., minor peak at 79.2 min., 11% ee.

Typical catalyzed procedure for allylation: **4.29b, 4.30a** and **4.30b**

In a flame dried flask was charged with dichloromethane (1.5 mL), freshly distilled benzaldehyde (37 μL, 0.36 mmol, 1.1 equiv) was added. The mixture was then cooled to –78 °C and the catalyst was added (triflic acid 3 μL, 0.03 mmol, 10 mol% or Sc(OTf)$_3$,15 mg, 0.03 mmol, 10 mol%). A solution of boronic ester **4.24** (100 mg, 0.33 mmol, 1.0 equiv) in 0.5 mL dichloromethane was prepared and added drop wise to the flask containing benzaldehyde at –78 °C. The reaction mixture was stirred at –78 °C for 40 hours, then quenched at –78 °C with 1.5 mL of aqueous saturated sodium bicarbonate and brought to room temperature over 3 hours. The phases were separated and the aqueous phase was extracted three times with dichloromethane. The combined organic phases were washed once with brine, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to afford the crude mixture. The ratio of compounds

4.29b and *E*-**4.30b** was determined by ^{1}H NMR of the crude mixture. The crude mixture was then purified by flash chromatography on silica gel using 80% hexanes : 20% ethyl acetate as eluent and afforded 25 mg (26%) of a mixture of compounds **4.29b** and *E*-**4.30b** (R*f*: 0.30, 20% ethyl acetate in hexanes).

4-(Dimethylphenylsilyl)-1-Phenyl-but-3-en-1-ol (4.29b)

This compound is known[35] and was prepared using $Sc(OTf)_3$ catalysis. Spectral data for **4.29b** are identical to those obtained for the product prepared using the thermal conditions. Spectral data can be found in reference 35.

HPLC: Chiralcel OD-RH, 60% *i*-PrOH/H_2O, 0.4 mL/min., UV detection at 210 nm, major peak at 61.1 min., minor peak at 79.2 min., 61% ee.

1-Phenyl-4-pinacolboronate-but-3-en-1-ol (4.30a)

This compound is known.[35] Spectral data for **4.30a** can be found in reference 35.

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.48-7.22 (m, 5H), 6.46 (dt, *J* = 18.0, 6.6 Hz, 1H), 5.53 (d, *J* = 18.0 Hz, 1H), 5.16 (t, *J* = 7.6 Hz, 1H), 3.31-2.98 (m, 2H), 1.25 (s, 12H);

^{13}C NMR (125 MHz, $CDCl_3$) δ = 149.3, 139.7, 128.7, 128.4, 128.0, 127.1, 79.6, 47.1, 29.7, 24.7.

1-Phenyl-*E*-4-[(1*R*,2*S*,3*R*,4*S*)-2,3-O-(boryl)-2-phenyl-1,7,7-trimethylbornanediol]-but-3-en-1-ol (*E*-4.30b)

This compound was not isolated from the crude mixture. The following ^{1}H NMR signals were used for the assignment of the product ratio of **4-29b** and ***E*-4.30b**.

4-29b: 5.85 ppm 1H

***E*-4.30b**: 5.52 ppm, 1H

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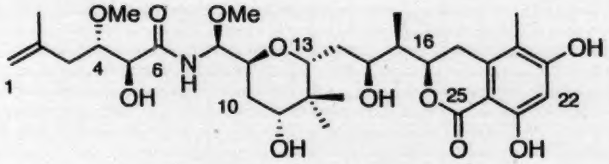
Chapter 5

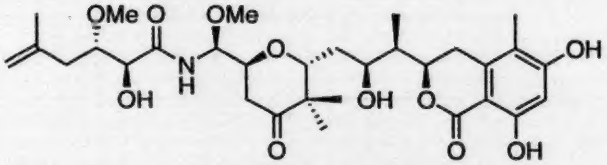
Synthetic Studies Towards Psymberin

5.1 Introduction

The isolation of natural products from marine organisms has provided organic chemists with numerous challenges and opportunities to develop new cures for diseases of great consequences such as AIDS, hepatitis C, and cancer. Psymberin (**5.1**), a naturally occurring polyketide, was isolated independently by two groups.[1,2] The group of Crews reported in 2004 the isolation of psymberin (**5.1**) from a sea sponge from the waters of Papua New Guinea, *Psammocinia sp.*[1] Around the same time, the group of Pettit also reported the isolation of irciniastatin A (psymberin) (**5.1**) from the Indo-Pacific marine sponge *Ircinia ramosa.*[2] In the same publication, Pettit also described the isolation of a related structure, irciniastatin B (**5.2**) (Figure **5-1**).



psymberin, irciniastatin A (**5.1**)



irciniastatin B (**5.2**)

Figure 5-1 Structures of Psymberin and Irciniastatin B

According to Crews and co-workers, psymberin possesses very interesting biological properties.[1] In their report, psymberin was tested against a panel of 60 human cancer cell lines and displayed an unusual pattern of activity (Table **5-1**). Psymberin was specific towards solid tumor cell lines. These results revealed a high level of selectivity towards melanoma cell lines, with LC_{50} in the nanomolar range. The tests also showed psymberin activity against some breast and colon cancer cell lines. Interestingly, psymberin was found to be rather inactive against leukemia cell lines (all activities $>2.5 \times 10^{-5}$ M).

Table 5-1. Bioactivity of Psymberin According to Crews and Co-Workers.[1]

cell line	LC_{50} (M)	cell line	LC_{50} (M)
leukemia		melanoma	
CCRF-CEM	$>2.5 \times 10^{-5}$	LOX IMVI	$>2.5 \times 10^{-5}$
HL-69(TB)	$>2.5 \times 10^{-5}$	MALME-3M	$<2.5 \times 10^{-9}$
K-562	$>2.5 \times 10^{-5}$	SK-MEL-2	$>2.5 \times 10^{-5}$
MOLT-4	$>2.5 \times 10^{-5}$	SK-MEL-5	$<2.5 \times 10^{-9}$
RPMI-8226	$>2.5 \times 10^{-5}$	SK-MEL-28	1.41×10^{-5}
SR	$>2.5 \times 10^{-5}$	UACC-257	$>2.5 \times 10^{-5}$
		UACC-62	$<2.5 \times 10^{-9}$
breast cancer		colon cancer	
MCF7	$>2.5 \times 10^{-5}$	HCC-2998	3.76×10^{-7}
HS 578T	$>2.5 \times 10^{-5}$	HCT-116	$<2.5 \times 10^{-9}$
MDA-MB-435	$<2.5 \times 10^{-9}$	HT29	$>2.5 \times 10^{-5}$
NCI/ADR-RES	1.9×10^{-5}	SW-620	$>2.5 \times 10^{-5}$
T-47D	1.36×10^{-5}		

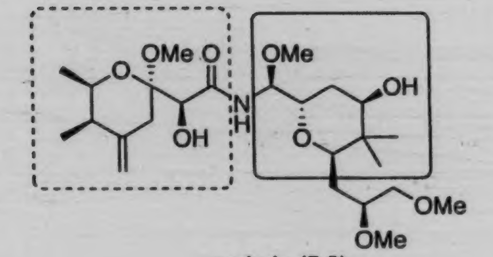
In the assays performed in the Pettit laboratory,[2] psymberin (**5.1**) and irciniastatin B (**5.2**) also displayed interesting biological activities as summarized in Table **5-2**.

Table 5-2. Bioactivity of Psymberin and Irciniastatin B by Pettit and Co-Workers.[2]

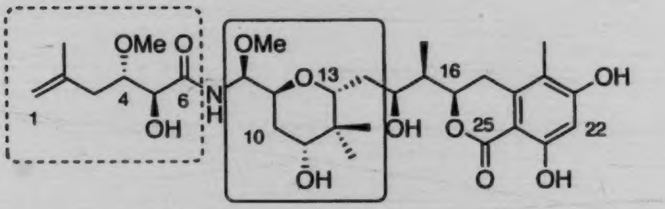
human cancer cell line		GI_{50} (μg/mL)	
		psymberin	irciniastatin B
pancreas	BXPC-3	0.0038	0.00073
breast	MCF-7	0.0032	0.00050
CNS	SF268	0.0034	0.00066
lung	NCI-H460	<0.0001	0.0012
colon	KM20L2	0.0027	0.0021
prostate	DU-145	0.0024	0.0016
murine leukemia	P388	0.00413	0.006

These results highlighted some interesting trends about these two natural polyketide anticancer molecules. The first observation was that irciniastatin B was as active as psymberin against colon and prostate cancers as well as against murine leukemia cells. In the screening for pancreatic, breast, and CNS cancers, irciniastatin B was more active than psymberin by one order of magnitude (i.e. 10 fold). This difference in activity was inverted in the case of lung cancer where psymberin was at least ten times more potent than irciniastatin B. In this study, psymberin has also shown a strong antivascular activity (<0.0005 mg/mL against HUVEC cells) and marginal antimicrobial activity.

Both psymberin and irciniastatin B are related to a large family of natural products, the pederin family,[3] which includes more than 35 related structures.[4] The compound pederin (**5.3**) is a good example of this family, and the close similarities with psymberin are depicted in Figure **5-2**. They both possess a pyran ring with similar substitution and stereochemistry. The amide side chains are also closely related. The pederins have also demonstrated anticancer activity but they did not display any sign of selectivities towards solid tumor cell lines as it was observed in the case of psymberin. This specific profile of activity is thought to come from the aromatic side chain of psymberin.



pederin (**5.3**)



psymberin, irciniastatin A (**5.1**)

Figure 5-2 Similarities Between Pederin and Psymberin

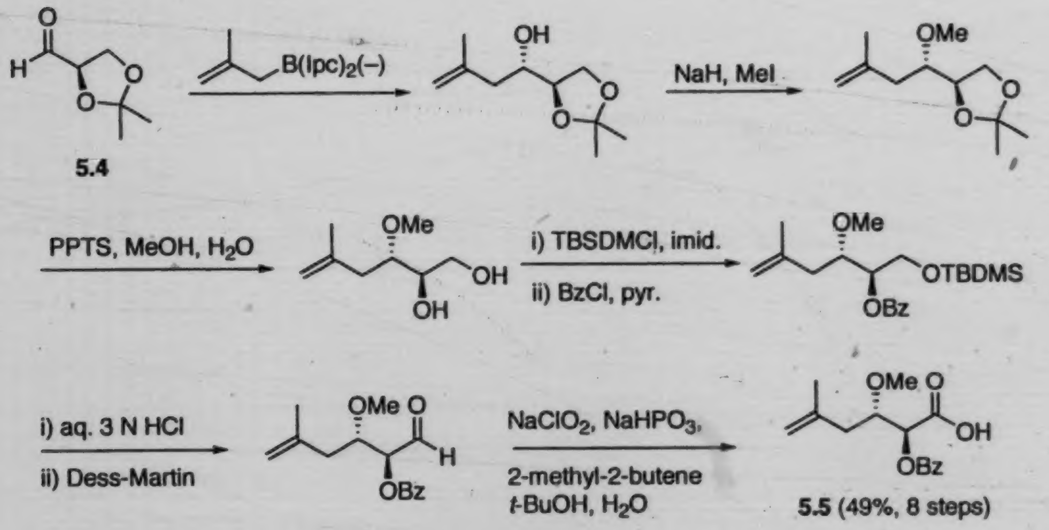
The pederins have been extensively studied for their synthesis,[3] biological activity,[3] and their biosynthesis.[5]

5.1.1 Current syntheses of psymberin

In the case of psymberin, very little work has been reported except for the above mentioned isolation papers. In the initial papers, the stereochemistry at carbon C4 was uncertain. To ascertain the configuration of this center, two partial syntheses were published to complete the final stereochemical assignment of psymberin.[6,7] The only other partial synthesis deals with the synthesis of the N7-C25 fragment and was published by Floreancig and co-workers.[8]

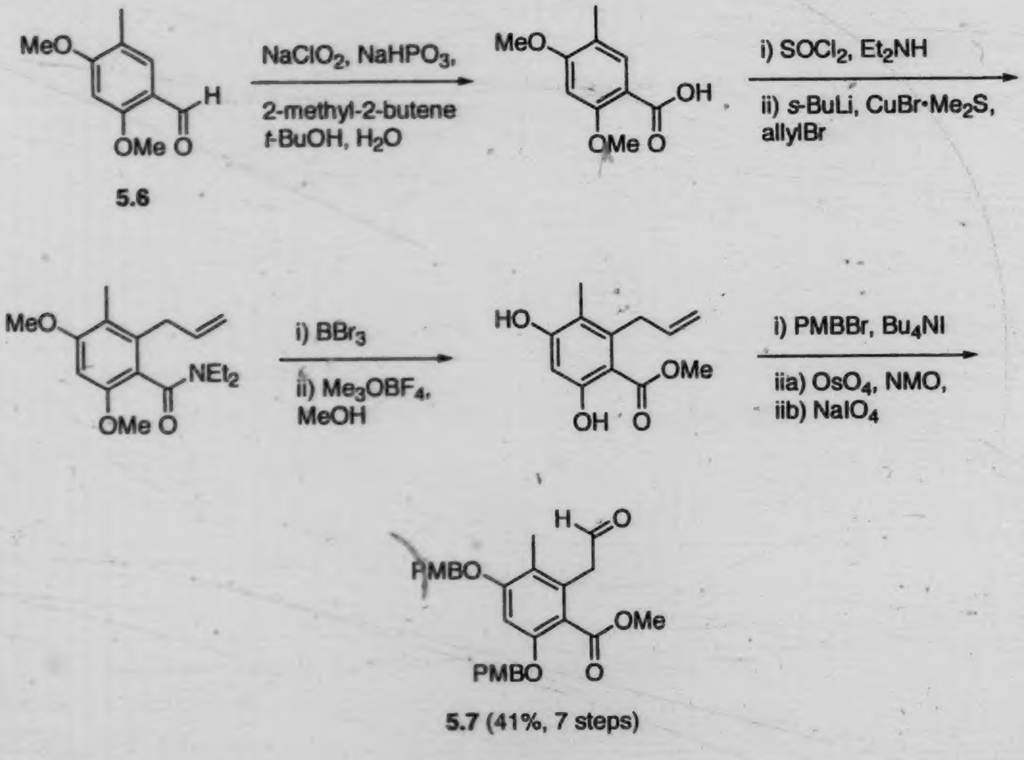
To date, only one complete total synthesis has been reported by the group of De Brabander. This remarkable achievement is described in Scheme **5-1** to Scheme **5-4**.[9] Their work confirms the relative and absolute stereochemistry assigned through the partial syntheses.

De Brabander's synthesis required the preparation of key intermediates **5.5**, **5.7**, and **5.9**. The first intermediate **5.5** was prepared from known aldehyde **5.4** using Brown's (–)-diisopinocampheyl methallyl borane as the key step to access the desired product in 70% yield and 95:5 d.r. This reaction was followed by a series of protections and deprotections, then completed by an oxidation to afford the acid **5.5** in 8 steps and 49% overall yield (Scheme **5-1**).


5.4
B(Ipc)2(–)
OH
NaH, MeI
OMe
PPTS, MeOH, H2O
OH
i) TBSDMCl, imid.
ii) BzCl, pyr.
OTBDMS
OBz
i) aq. 3 N HCl
ii) Dess-Martin
OMe O
H
NaClO2, NaHPO3,
2-methyl-2-butene
t-BuOH, H2O
5.5 (49%, 8 steps)

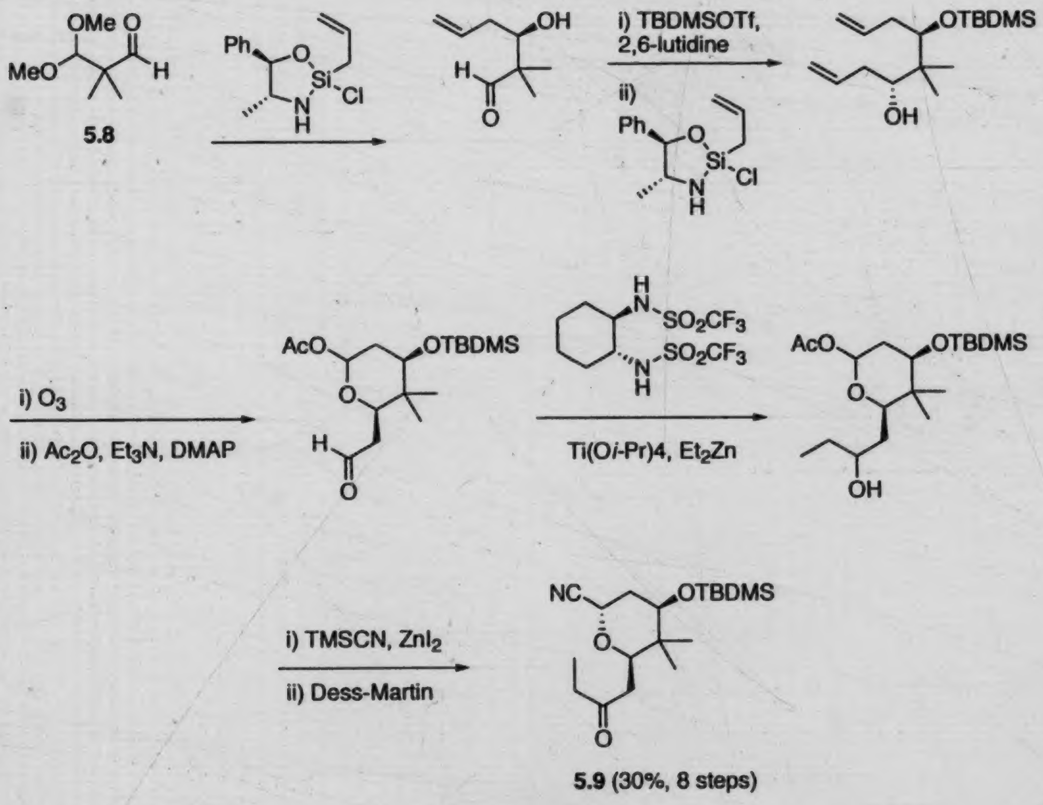
Scheme 5-1

The second key fragment was aldehyde **5.7**. This intermediate was obtained from the known compound **5.6** in 7 steps with an overall yield of 41% (Scheme **5-2**). From aldehyde **5.6**, an oxidation was carried out to generate the corresponding acid, which was then transformed into an amide. This was followed by directed *ortho*-metallation and reaction with allyl bromide. The amide was hydrolyzed to the acid, which was esterified into its methyl ester. Finally, ozonolyzis of the allyl group led to intermediate **5.7**.


MeO
H
OMe O
5.6
NaClO2, NaHPO3,
2-methyl-2-butene
t-BuOH, H2O
MeO
OH
OMe O
i) SOCl2, Et2NH
ii) s-BuLi, CuBr•Me2S, allylBr
MeO
NEt2
OMe O
i) BBr3
ii) Me3OBF4, MeOH
HO
OMe
OH O
i) PMBBr, Bu4NI
iia) OsO4, NMO,
iib) NaIO4
H
O
PMBO
OMe
PMBO O
5.7 (41%, 7 steps)

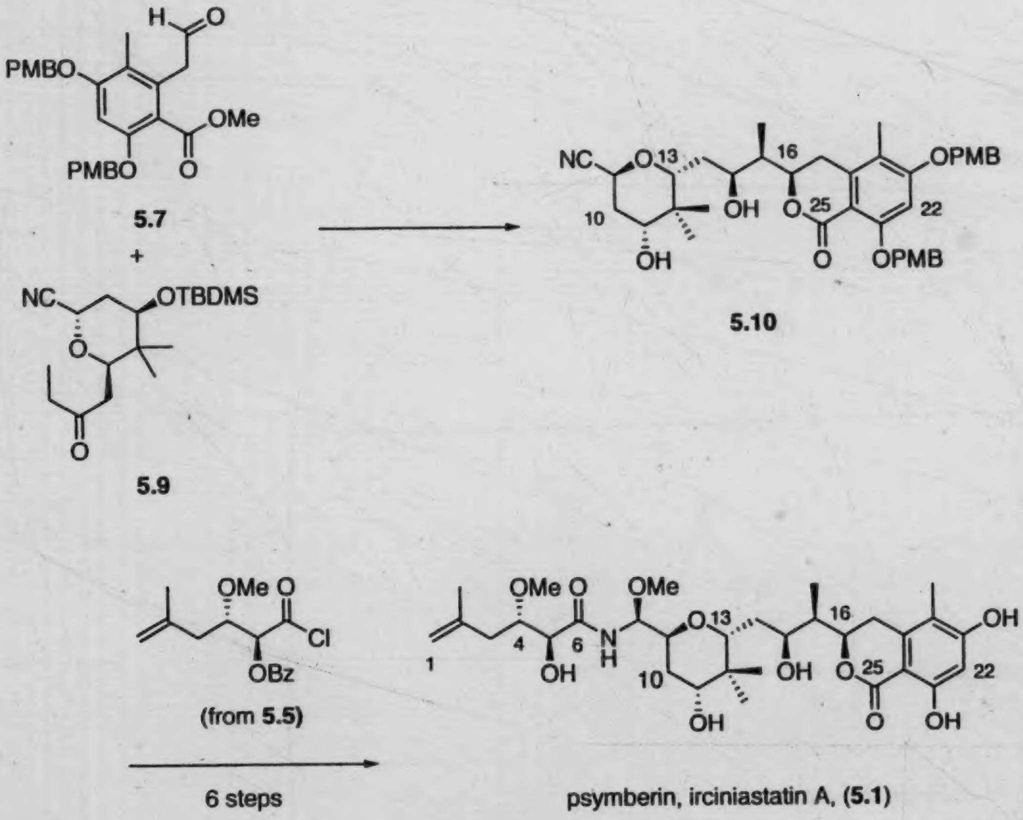
Scheme 5-2

The remaining fragment **5.9** was prepared in 8 steps with an overall yield of 30% (Scheme **5-3**). This portion was prepared from starting material **5.8** using, as key steps, a series of two Leighton's allylsilation reactions to introduce the stereogenic centers at C11 and C13. These two key steps were then followed by ozonolysis, acetylation, addition of diethyl zinc, oxidations, and reaction with TMSCN to produce the desired nitrile **5.9**. The preparation of intermediate **5.9** in such a low yield will prove to be one of the limitations of this synthesis.


OMe O
MeO
H
5.8
Ph
O
Si
Cl
N
H
OH
H
O
i) TBDMSOTf, 2,6-lutidine
ii)
Ph
O
Si
Cl
N
H
OTBDMS
OH
i) O₃
ii) Ac₂O, Et₃N, DMAP
AcO
OTBDMS
O
H
O
H
N
SO₂CF₃
SO₂CF₃
N
H
Ti(O*i*-Pr)4, Et₂Zn
AcO
OTBDMS
O
OH
i) TMSCN, ZnI₂
ii) Dess-Martin
NC
OTBDMS
O
O
5.9 (30%, 8 steps)

Scheme 5-3

In the final assembly of the fragments to complete the synthesis (Scheme 5-4), the junction between C15 and C16 was achieved through a boron mediated aldol reaction between **5.7** and **5.9**. Intermediate **5.10** was obtained in good yield (88%) and good diastereomeric ratio (12:1). Further transformations and attachment of the acyl side chain, using the acyl chloride derived from **5.5**, was followed by final removal of the benzoate and *p*-methoxybenzyl protecting groups to afford psymberin (**5.1**).



Scheme 5-4

This convergent synthesis provided synthetic psymberin (**5.1**) in 8.3% overall yield in the longest linear sequence of 17 steps. The introduction of the acyl side chain with concomitant formation of the α-alkoxycarboxamide followed by global deprotection provided a 2:1 mixture of the desired diastereoisomer of psymberin. The lack of selectivity in that final key step significantly reduced the yield of this transformation to 56%.

5.2 Retrosynthesis

The structural features of psymberin, its unusual profile of bioactivity, its novelty, and its initial stereochemical uncertainties made it a very attractive synthetic target. Psymberin also seemed to be an ideal target to which we could apply new methodologies developed in our laboratory. From the natural product structure, we envisioned two convergent disconnections (Figure **5-3**). First, a Curtius rearrangement between fragments **5.11** and **5.12** could provide us with the α-alkoxycarboxamide. Since this reaction is stereospecific, we should be able to have control on the stereochemistry at C8. This type of rearrangement has been used in the synthesis of the related compound theopederin D.[3] The disconnection on the aromatic side of psymberin could come from alkylation chemistry on an acetal of the type of **5.12**. This would allow for its connection with fragment **5.13**.

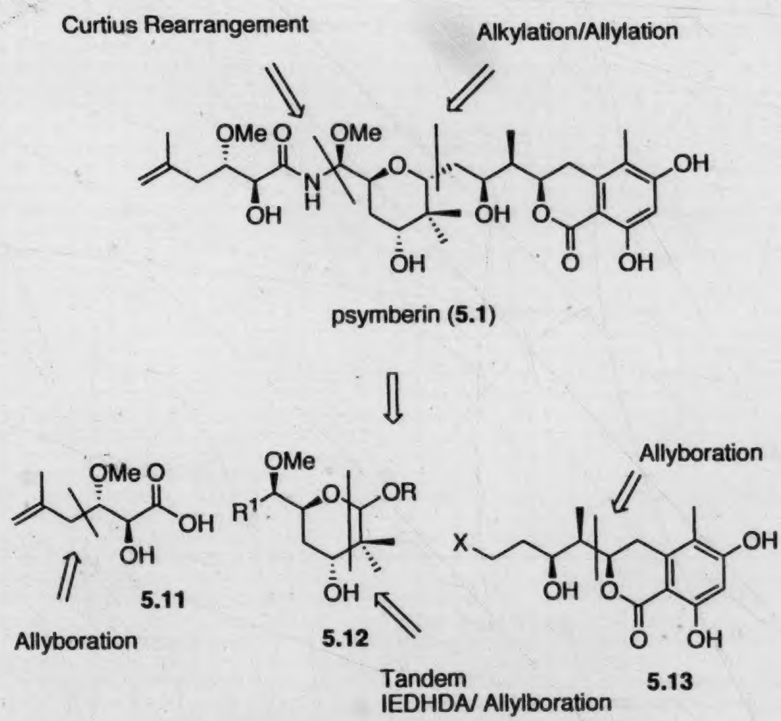

Curtius Rearrangement
Alkylation/Allylation
psymberin (5.1)
5.11
Allyboration
5.12
Tandem
IEDHDA/ Allylboration
Allyboration
5.13

Figure 5-3 Retrosynthesis of Psymberin

The first intermediate **5.11** could be obtained through a Lewis acid-catalyzed allylboration using the methallylation reagent **5.14** (**2.2a** Chapter 2) on α-chiral aldehyde **5.15** functionalized with the appropriate protecting groups (Figure **5-4**).

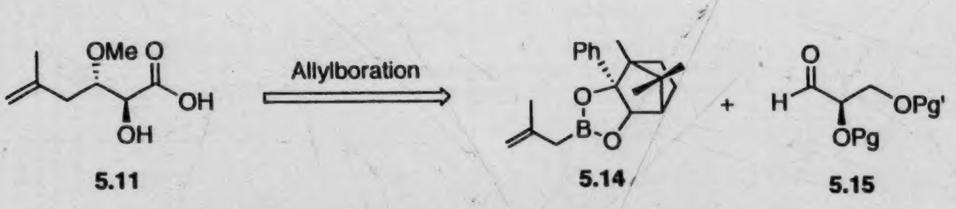

5.11
Allylboration
5.14
5.15

Figure 5-4 Retrosynthesis of Fragment **5.11**

To access the key intermediate **5.12**, a substrate of the type of **5.16** could undergo an inversion of the hydroxyl group in the presence of a suitable nucleophile. The selective oxidation of the alkene would need to be carried out followed by the introduction of an appropriate hydroxyl protecting group. This compound, **5.16**, could be obtained through a tandem inverse-electron-demand-hetero-Diels-Alder (IEDHDA)/allylboration reaction between boronoacrolein **5.18**, the trisubstituted enol ether **5.19**, and glyoxalate **5.17**. This methodology has previously been developed by Xuri Gao in the Hall laboratory (Figure **5-5**).[10] The use of a 2,2-disubstituted enol ether, however, would constitute a new challenge that has not yet been addressed in the context of this method.

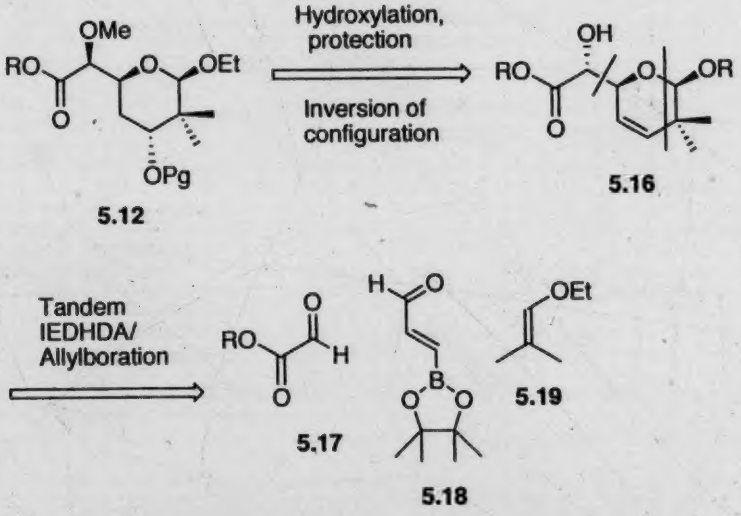

OMe
RO
O
O
OEt
OPg
5.12
Hydroxylation, protection
Inversion of configuration
OH
RO
O
O
OR
5.16
Tandem IEDHDA/ Allylboration
RO
O
O
H
5.17
H
O
B
O
O
5.18
OEt
5.19

Figure 5-5 Retrosynthesis of Fragment **5.12**

Intermediate **5.13** could possibly come from a second Lewis acid-catalyzed allylboration between *Z*-crotylboronate **5.20** and aromatic aldehyde **5.21** (Figure **5-6**).

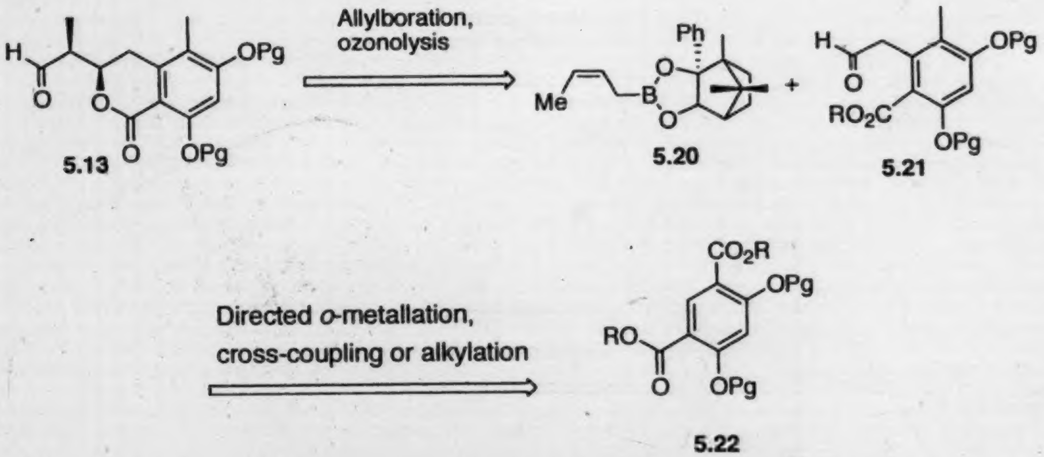
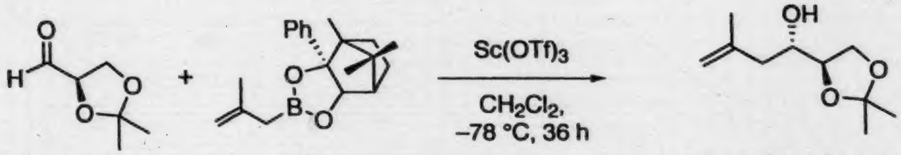

5.13
Allylboration,
ozonolysis
5.20
5.21
Directed o-metallation,
cross-coupling or alkylation
5.22

Figure 5-6 Retrosynthesis of Fragment **5.13**

This aromatic aldehyde could be obtained through directed *ortho*-metallation of **5.21** and either cross-coupling chemistry or alkylation of the intermediate (Figure **5-6**). Aromatic precursor **5.22** could be prepared from commercially available resorcinol via protection, bromination, followed by two lithium-halogen exchanges reacted sequentially with methyl iodide and carbon dioxide.

5.2.1 Synthesis of fragment 5.11

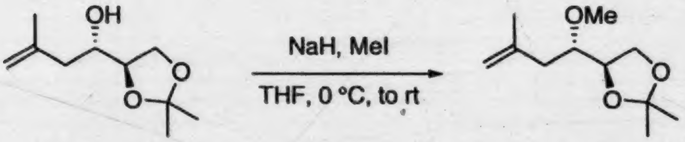
The proposed approach to the first fragment **5.11** was initiated using aldehyde **5.4**[11] and methallylboronate **5.23** (Equation **5-1**). This reaction involves the addition of a chiral allylic species to an α-chiral aldehyde, a situation that gives rise to two possible reagent combinations. The first case is when both the allylic boronate reagent and the chiral aldehyde favor the formation of the same diastereoisomer; this is referred to as the "matched" case. The second case is when the reagent and the chiral aldehyde are opposing each other; this is referred to as the "mismatched" case. As discussed in Chapter 1 (Section **1.4.1.3**) the prediction of matched and mismatched situation greatly varies depending on the nature of the α-substituent on the aldehyde component. In most cases, it is needed to investigate both enantiomers of the allylic boronate species to identify the optimal reagent to obtain the desired addition product. The Lewis acid-catalyzed allylboration method was carried out,[12,13] and the desired product **5.24** was obtained in good yield (75%) and excellent diastereisomeric ratio. Only one diastereoisomer was observed in the crude ^{1}H NMR spectrum (>49:1 d.r.) (Scheme **5-1**). When this reaction was performed on a large scale (two grams of boronate **5.23**), a slightly longer reaction time of 36 hours was required.



5.4 **5.23** **5.24** (75%, >49:1 d.r.)

Equation 5-1

The purified alcohol **5.24** was methylated using sodium hydride and methyl iodide in THF and afforded the desired product **5.25** in 85% yield (Equation **5-2**).

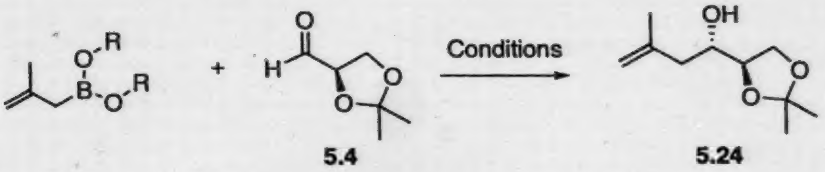


5.24 **5.25** (85%)

Equation 5-2

Thus, the obtained protected alcohol can be transformed into acid **5.11** in the same sequence used by De Brabander and co-workers (Scheme **5-1**).[9]

Since the reaction between methallylboronate **5.23** and α-chiral aldehydes was not investigated in our initial studies (Chapter 2), we explored the effect of catalysis on the addition of methallyl reagents to aldehyde **5.4** (Equation **5-3** and Table **5-3**). When pinacol methallylboronate was reacted at room temperature without any catalyst, the quick reaction provided product **5.24** with no selectivity (5:4 d.r.). When the same reagent was used at −78 °C, under the catalytic manifold, the same product **5.24** was obtained with increased selectivity (5:1 d.r.). In the case where the *R*-enantiomer of the camphor-derived diol was used, the opposite diastereoisomer of **5.24** was obtained in poor selectivity (1:2 d.r.). This stereochemical outcome was the result of a mismatched addition and showed that the methallylboration reagent was not able to efficiently override the intrinsic bias of the aldehyde. In contrast, when the matched reaction was performed using the *S*-enantiomer of the diol, the desired product **5.24** was obtained in a single diastereoisomer and 75% yield. Fortunately, for the synthesis of psymberin, intermediate **5.24** from the matched combination of substrate and reagent was required.



Equation 5-3

Table 5-3. Addition of Methallylboronates to Aldehyde **5.4** (Equation **5.3**).

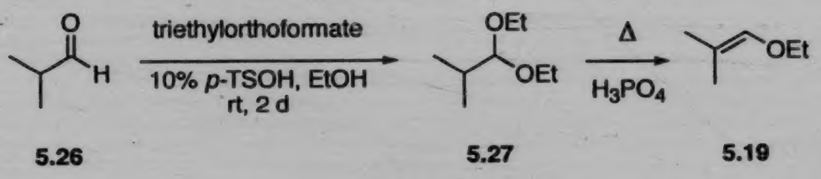
boronate (*OR*)	conditions	d.r. (yield)
Pinacol	CH_2Cl_2, rt	5:4
Pinacol	CH_2Cl_2, $Sc(OTf)_3$, –78 °C	5:1
(*R*)-Camphor diol	CH_2Cl_2, $Sc(OTf)_3$, –78 °C	1:2
(*S*)-Camphor diol	CH_2Cl_2, $Sc(OTf)_3$, –78 °C	>49:1 (75)

5.2.2 Synthesis of fragment 5.12

For the synthesis of fragment **5.12**, two approaches were examined. Both of these strategies made use of the tandem IEDHDA/allylboration reaction. One used the trisubstituted enol ether **5.19** (Figure **5-5**), and the second one used the monosubstituted enol ether **5.39** (Scheme **5-11**) with the intent of introducing the second methyl group through enolate chemistry at a later point in the synthesis.

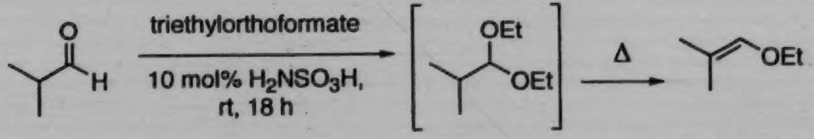
The tandem IEDHDA/allylboration reaction has proven to be a reliable reaction that can be applied to natural product synthesis.[14] Unfortunately, to the best of our knowledge, no report of the use of Jacobsen's Cr(III) catalyst[15] to the IEDHDA reaction with a trisubstituted enol ether has been published.

To be able to investigate the possibility of using the trisubstituted enol ether **5.19** in the synthesis of key fragment **5.12**, a convenient preparation of the enol ether was to be developed. For our first attempt at this intermediate, a two step procedure starting from isobutyraldehyde (**5.26**) was carried out (Scheme 5.5).[16,17] Isobutyraldehyde (**5.26**) was reacted for two days with triethylorthoformate in the presence of a catalytic amount of *p*-toluenesulfonic acid. Distillation of **5.27** in the presence of a catalytic amount of phosphoric acid (one drop) effected the elimination of ethanol from acetal **5.27** to form enol ether **5.19**. This sequence only gave poor yields (<20%), and mainly decomposition was observed during the ethanol elimination step. Increasing the amount of phosphoric acid provided only a marginal improvement to the yield. The problem appeared to come from the presence of residual ethanol after the distillation that provided acetal **5.27**.



Scheme 5-5

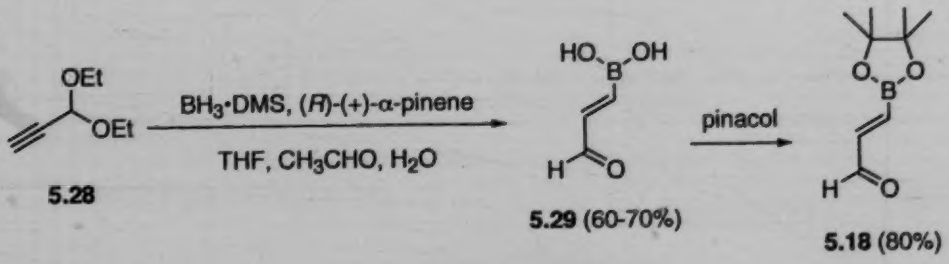
To circumvent this problematic distillation, alternative procedures were investigated. A particularly interesting example involved the use of catalytic sulfamic acid. In this procedure, the catalyst is easily removable by simple filtration. Thus, when isobutyraldehyde (**5.26**) was stirred in neat triethylorthoformate with 10 mol% of sulfamic acid at room temperature, acetal formation was completed after 18 hours. Since all known preparations of the enol ether involved acid catalyzed elimination of ethanol, instead of performing the simple filtration of insoluble sulfamic acid, we decided to attempt the distillation immediately (Scheme **5-6**). Although this distillation proved to be challenging (boiling points: ethyl formate: 52-54 °C, isobutyraldehyde: 63 °C, ethanol: 78 °C, enol ether **5.19**: 92-94 °C, acetal **5.27**: 133-134 °C), it was possible to obtained pure enol ether **5.19** when two distillations were performed. The first distillation was performed with a long vigreux column and then followed by a short path distillation apparatus, and extraction (3 times) with 1% aqueous K_2CO_3. The desired enol **5.19** was obtained in about 60% yield, containing only traces of ethyl formate. The enol ether was stored for weeks in a freezer over solid K_2CO_3 with no changes in purity (see experimental section for details).



5.26 **5.27** **5.19** (60%)

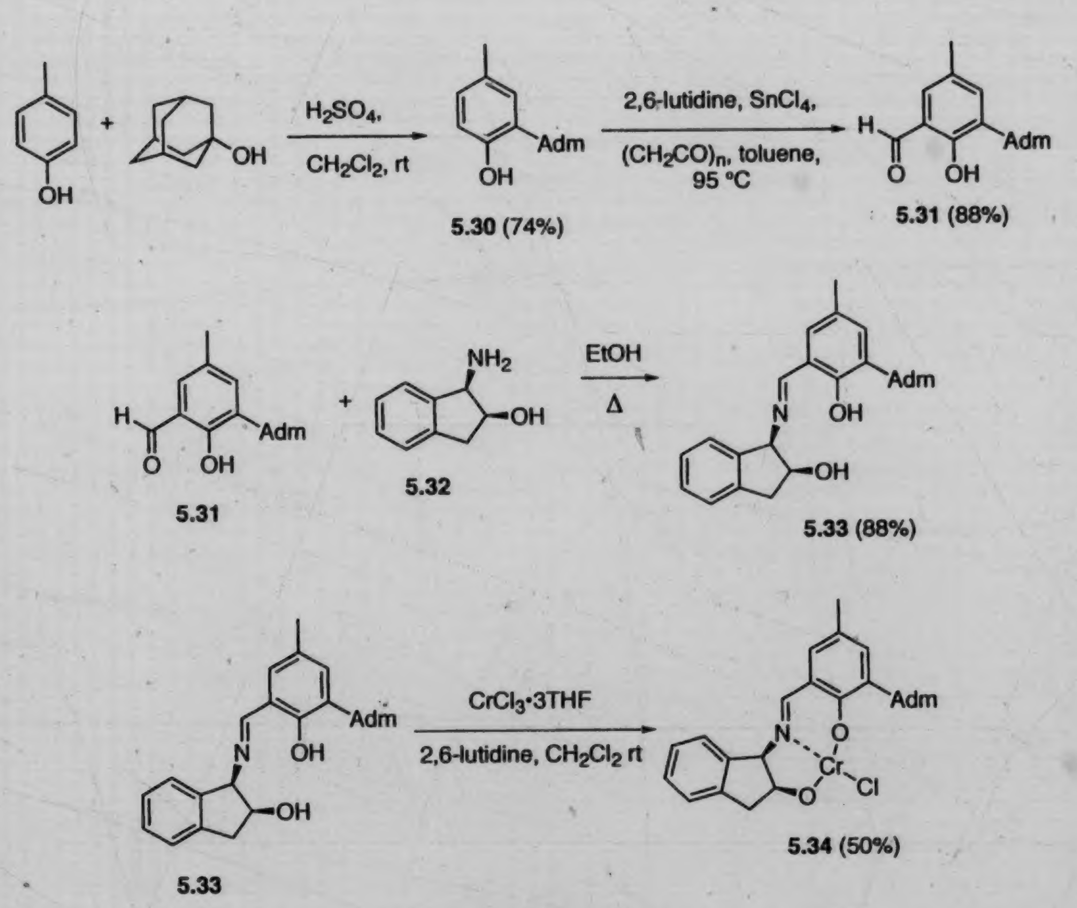
Scheme 5-6

With the desired enol ether now available, we could explore the key tandem IEDHDA/allylboration reaction. The required heterodiene **5.18** was synthesized from commercially available propargylaldehyde diethyl acetyl (**5.28**) according to the literature procedure (Scheme **5-7**).[18] The alkynyl substrate was treated under hydroboration conditions involving (*R*)-(+)-α-pinene, with borane dimethylsulfide. When the reaction was completed, the hydroboration product was reacted with acetaldehyde to generate boronic acid **5.29** in yields typically between 60 to 70%. This boronic acid was kept in a desiccator for up to four weeks without any significant decomposition. The boronoacrolein pinacolate **5.18** was prepared fresh before each use by mixing a slight excess of the boronic acid and pinacol together in tetrahydrofuran and simply coevaporated three times.



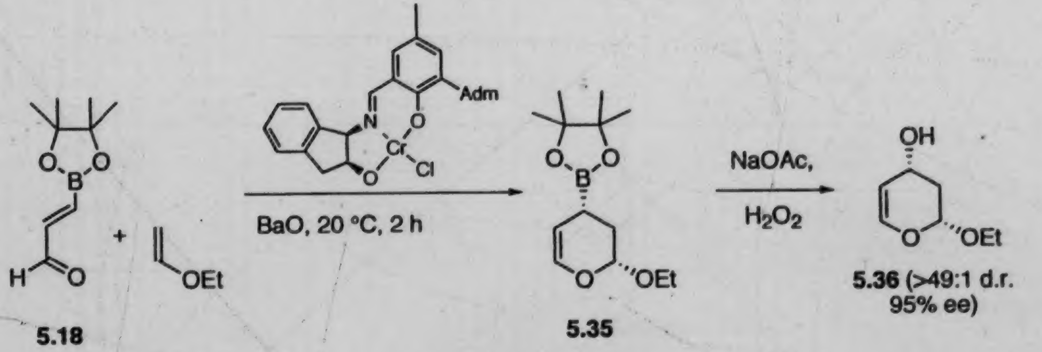
Scheme 5-7

The chiral chromium catalyst **5.34** required for the IEDHDA reaction was prepared according to Jacobson's procedure[15] as described in Scheme **5-8**. Firstly, *p*-cresol was reacted with 1-adamantanol in the presence of sulfuric acid to provide phenol **5.30** in good yield (74%). This phenol was then formylated using paraformaldehyde and tin tetrachloride to give the benzaldehyde **5.31** in 88% yield. The reaction of the aldehyde **5.31** with 1*R*,2*S*-(+)-*cis*-1-amino-2-indanol (**5.32**) in ethanol at reflux provided the desired ligand **5.33** in 88% yield. Finaly, the reaction of the ligand **5.33** with chromium trichloride tris-tetrahydrofuran complex in dichloromethane provided us with a sample of the pure catalyst **5.34**. In my hands, only the yield of the last step was lower than the one reported by Jacobsen.[15] It was possible to obtain a yield closer to the reported values by getting a second crop of the catalyst from the mother liquors but each time, the quality of this second crop was lower and provided lower selectivity in the test reaction with ethyl vinyl ether (Scheme **5-9**).


H_2SO_4,
CH_2Cl_2, rt
OH
Adm
5.30 (74%)
2,6-lutidine, $SnCl_4$,
$(CH_2CO)_n$, toluene, 95 °C
H
O
5.31 (88%)
NH_2
5.31
5.32
EtOH
Δ
N
5.33 (88%)
$CrCl_3$•3THF
2,6-lutidine, CH_2Cl_2 rt
Cr
Cl
5.33
5.34 (50%)

Scheme 5-8

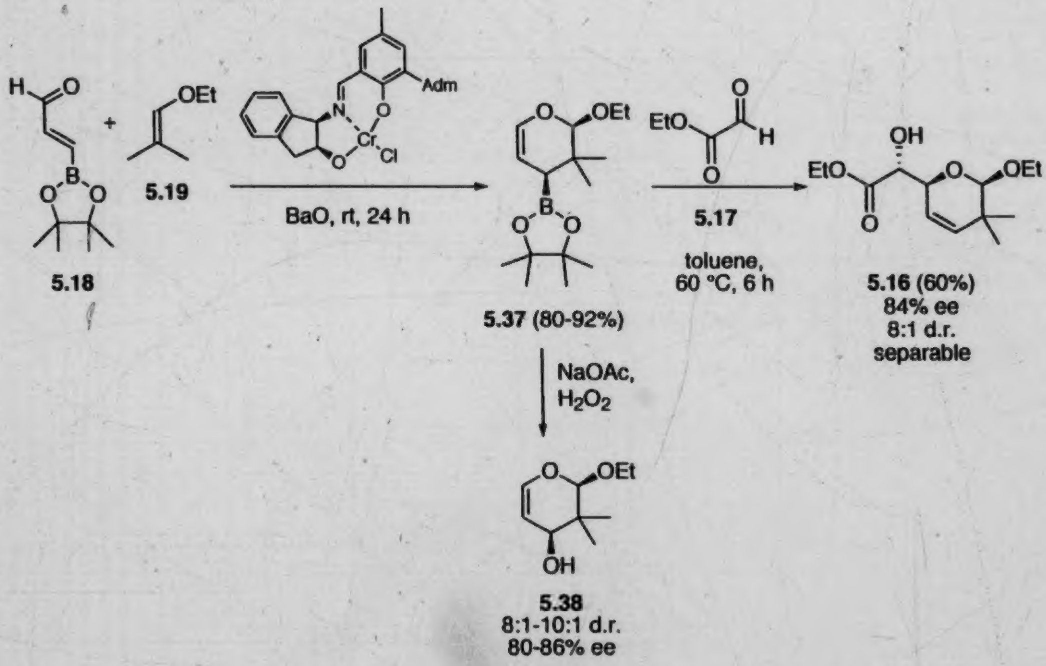
To ascertain the quality of each batch of the complex **5.34**, the newly prepared catalyst was used in the test reaction described in Scheme **5-9**.[10] To this end, the commercially available ethyl vinyl ether was treated with boronoacrolein pinacolate (**5.18**) at 20 °C for two hours in the presence of barium oxide and the catalyst without any solvent. The crude reaction mixture containing cyclic boronate **5.35** was oxidized using sodium acetate and hydrogen peroxide to produce alcohol **5.36**. This alcohol was then analyzed using chiral HPLC to determine the level of selectivity obtained with each batch of catalyst. The product of the oxidation reaction was found to be highly volatile.



Scheme 5-9

With all the starting materials now available for the synthesis, it was possible to test the key transformation, the tandem IEDHDA/allylboration reaction (Scheme **5-10**). It was found that the first step required a significantly longer reaction time (24 hours) compared to the two hours required in the test reaction with ethyl vinyl ether. This difference is due to the increased steric interactions between the two terminal methyl groups and the chiral catalyst. It is also in perfect concordance with observations made by Gao and Hall,[19] who found that the *cis*-enol ether reacted relatively slowly compare to the unsubstituted enol ether, ethyl vinyl ether (5 h vs. 2 h). The same *cis*-enol ethers also reacted significantly faster than their *trans*-isomers.

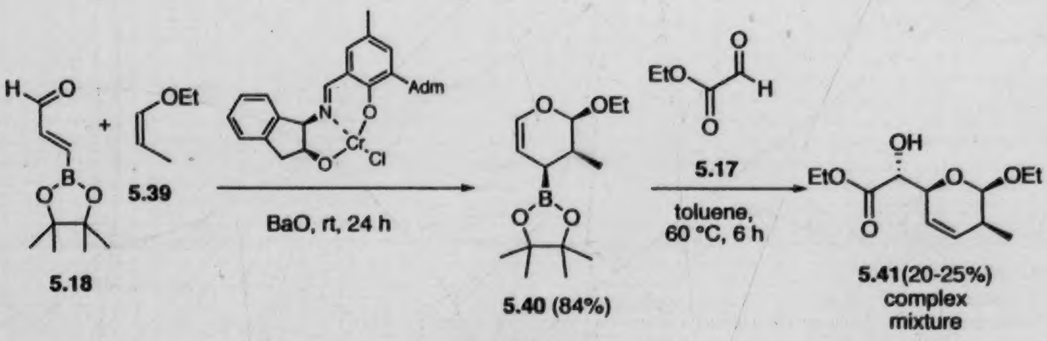
In the course of this reaction it was also found that the reaction with the trisubstituted enol ether gave rise to a small amount of diastereoisomer arising from the exo Diels-Alder process. The endo product was the major one with a ratio between 8:1 and 10:1. This is the result of increased steric interactions from the dienophile. It is worth mentioning that the achiral reaction using Yb(fod) as a catalyst provided the desired racemic product without any traces of the diastereomeric product. To determine the enantioselectivity of the reaction, the Diels-Alder product was oxidized under typical conditions (NaOAc and H_2O_2) to generate **5.38** and analyzed using chiral HPLC. The enantioselectivity of the hetero-Diels-Alder product was found to be between 80% and 86%. This was significantly lower than the 95% obtained in the test reaction with ethyl vinyl ether and in the case of monosubstituted enol ethers.[14,19] One crucial piece of information obtained was the sensitivity of the reaction to the purity of the enol ether. If it was not of sufficiently high purity, the reaction did not proceed well. When the starting enol ether contained any traces of ethanol, no Diels-Alder product was observed. In these cases, ethanol was probably acting as an excellent ligand for the chromium catalyst, sequestering it and subsequently deactivating it.


5.18
5.19
Adm
BaO, rt, 24 h
5.37 (80-92%)
5.17
toluene,
60 °C, 6 h
5.16 (60%)
84% ee
8:1 d.r.
separable
NaOAc,
H2O2
5.38
8:1-10:1 d.r.
80-86% ee

Scheme 5-10

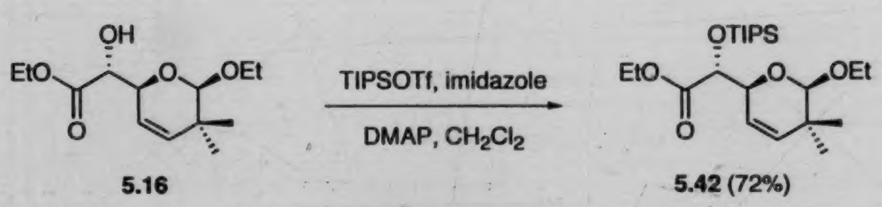
It was also found that the new Diels-Alder adduct had to be used in the subsequent allylboration reaction immediately after the removal of the catalyst. If the second reaction was not carried out right away, the product underwent what seemed to be a retro Diels-Alder reaction, as the ^{1}H NMR and ^{13}C NMR spectra showed the reappearance of the starting material peaks over a period of 18 hours (overnight). The Diels-Ader adduct was treated at 60 °C for six hours with ethylglyoxalate (**5.17**) to afford 60% of the desired product after purification. At this point, the undesired diastereoisomer coming from the Diels-Alder reaction was removed during silica gel chromatography. All efforts at running the allylboration reaction at lower temperatures failed. This reflected the fact that ethylglyoxalate exists as a polymer at room temperature and is cracked only at a temperature around 60 °C. When the reaction was run for longer periods of time, decomposition of the product was observed. Attempts to run the allylboration in a "one-pot" fashion were made but remained unsuccessful, leading mainly to a mixture of decomposition products and lower overall yield.

Since the tandem sequence with the enol ether **5.19** provided a moderate enantioselectivity (80-86%), we decided to investigate the possibility of using the simpler enol ether **5.39**, and introduce the second methyl group later in the synthetic sequence (Scheme **5-11**). This plan was quickly assessed as the enol ether is commercially available as a 3:1 mixture of isomers. It was proven by Gao and Hall[19] that this mixture was suitable for this reaction sequence. Indeed, the hetero-Diels-Alder reaction performed well but when the obtained adduct **5.40** was submitted to the allylboration reaction it only gave a low yield of **5.41** (20-25%) with a tedious purification. It was thought that this allylboration reagent (**5.39**), possessing only one methyl group, was probably more reactive and more sensitive than (**5.19**) with the geminal dimethyl group. These two factors are incompatible with the allylboration reaction, which requires heating the aldehyde to 60 °C in order to crack its polymeric form. This approach was abandoned since it provided such a low yield of product and required an extra step in the synthesis to introduce the missing methyl group.


5.18
5.39
Adm
BaO, rt, 24 h
5.40 (84%)
5.17
toluene, 60 °C, 6 h
5.41(20-25%)
complex
mixture

Scheme 5-11

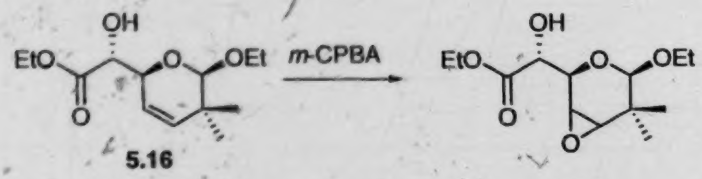
To be able to further transform the product obtained from the tandem sequence, protection of the alcohol was necessary (Equation **5-4**). A series of protecting groups were tested and amongst those tried, the triisopropylsilyl **5.42** (72% yield) group stood out as the best group to install on this hindered secondary alcohol.


5.16
TIPSOTf, imidazole
DMAP, CH2Cl2
5.42 (72%)

Equation 5-4

Functionalization of the alkene generated in the allylboration reaction was planned to proceed through an epoxide such as **5.43**. The epoxidation was first carried out on alkene **5.16** using *m*-chloroperoxybenzoic acid (Equation **5-5**).

After four days, this reaction provided epoxide **5.43** in good yield and only one diastereoisomer was observed by ^{1}H NMR.

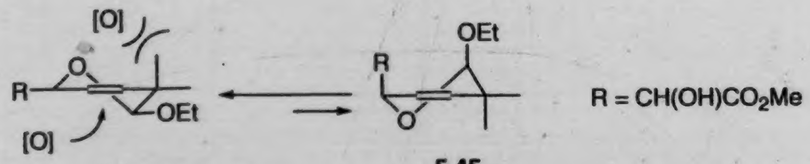


5.16

5.43

Equation 5-5

The relative stereochemistry of the obtained epoxide could not be assigned on the basis of TROESY NMR studies due to the overlap of many signals in the region of 3.5 ppm. Considering the conformations of alkene **5.16,** represented by **5.44** and **5.45**, **5.44** should be favored over **5.45** since it minimizes the number of axial groups (Figure **5-7**). Based on this, it was expected that the epoxidation reagent would most likely come from the bottom face. This approach avoids steric interactions between the incoming reagent and the axial methyl group.

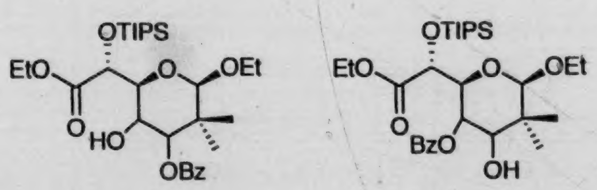


5.44

5.45

Figure 5-7 Conformations of Alkene **5.16**

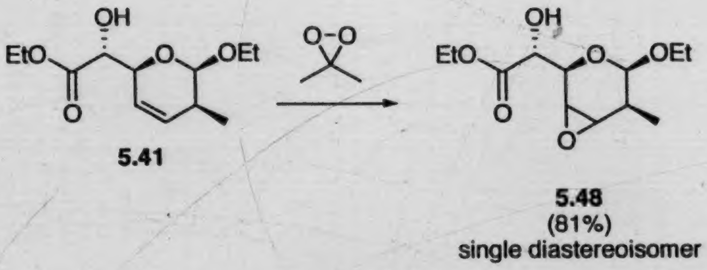
Unfortunately, this epoxidation procedure was rather slow, requiring up to four days until the starting material had completely disappeared. Unfortunately, when the same reaction was performed using alkene **5.42**, a significant side reaction was observed due to the long reaction time. The opening of the obtained epoxide by the liberated benzoate from *m*-CPBA to generate a product of the type of **5.46** or **5.47** (Figure **5-8**). This generated side product could not easily be used as an intermediate in our synthesis, therefore it was not investigated further.



5.46 **5.47**

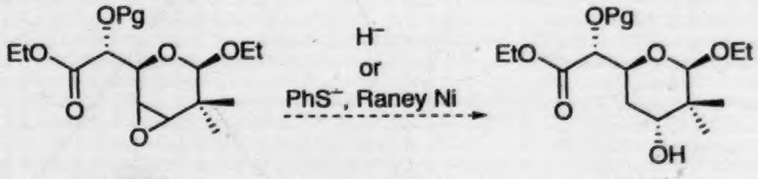
Figure 5-8 Structure of Side Products in *m*-CPBA Epoxidation

In an attempt to circumvent this unfortunate side reaction, other epoxidation procedures were also explored and a procedure using dimethyldioxirane (DMDO) was adopted, for many reasons. An important attribute of this reagent was its high level of reactivity, which would hopefully reduce the reaction time. This reagent does not generate any nucleophilic species, thus reducing the possibility of a side reaction as previously observed in the case of the *m*-CPBA epoxidation reaction. Considering that DMDO is not known to be a hydroxyl-directed oxidation reagent, this would possibly allow us to run the reaction directly on the unprotected alcohol. Methods to generate DMDO *in situ* are available,[20] thus eliminating the potentially dangerous distillation step. All these characteristics rendered the use of this reagent very attractive. The epoxidation of the free alcohol containing alkene **5.41** was attempted using these conditions. It quickly (<2 hours) and cleanly afforded the desired epoxidized product **5.48** (Equation **5-6**). Furthermore, only one diastereoisomer was observed in the ^{1}H NMR spectrum. As in the case discussed previously, it was impossible to assign the relative stereochemistry via 2D NMR experiments due to the overlapping signals. In addition, any attempts at obtaining crystals of sufficient quality have failed. The results obtained in the epoxidation with DMDO confirmed what we anticipated and seemed to be a more efficient procedure for the epoxidation of alkenes such as **5.16** and **5.41**.



Equation 5-6

To complete the synthesis of the key fragment **5.12**, two transformations remain. Firstly, selective opening of the epoxide **5.43**, then inversion of the hydroxyl group (Equation **5-7**). In the case of the epoxide opening, two possibilities are available, namely, direct opening using a hydride source such as DIBAL or a two step procedure first using a thiophenolate to open the epoxide followed by its reduction using Raney®-nickel.



5.42 **5.49**

Equation 5-7

In either case, we expect the nucleophile (H^- or PhS^-) to open the epoxide on the side leading to an axial attack process as shown in Figure **5-9**.

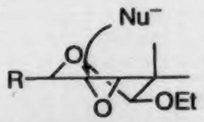
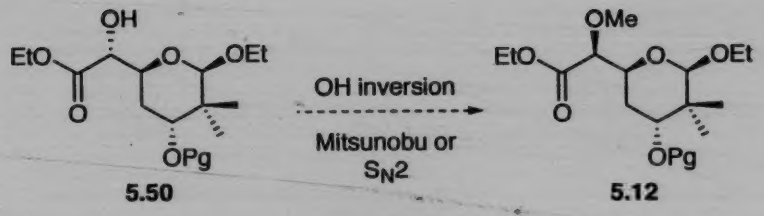


Figure 5-9 Preferred Nucleophilic Attack on Epoxide **5.43**

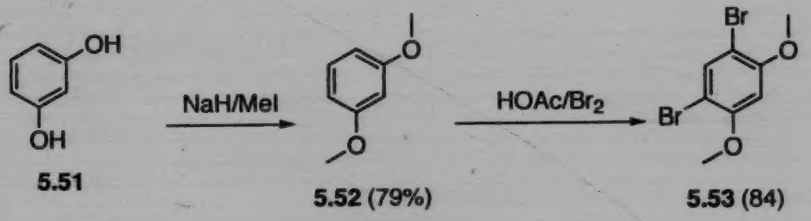
The final exocyclic hydroxyl group inversion is expected to proceed from **5.50** under Mitsunobu conditions using benzoate as nucleophile or through an S_N2 reaction process with a suitable nucleophile to produce key intermediate **5.12** (Equation **5-8**).


OH
EtO
O
OEt
O
OPg
5.50
OH inversion
Mitsunobu or
S_N2
OMe
EtO
O
OEt
O
OPg
5.12

Equation 5-8

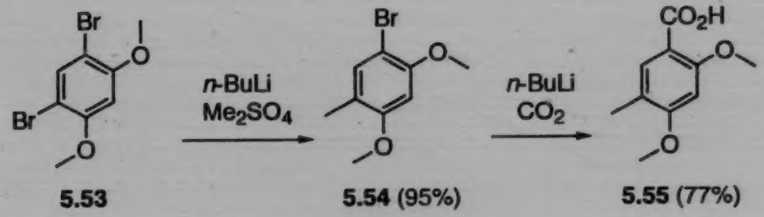
5.2.3 Synthesis of fragment 5.13

The synthesis of the remaining synthon **5.13**, leading to the aromatic side chain of psymberin, started from commercially available resorcinol **(5.51)**. Treatement of **5.51** with sodium hydride and methyl iodide gave dimethoxybenzene **5.52** in good yield (79%). The dibromination of **5.52** was effected by its treatment with bromine in acetic acid to provide the desired dibromide **5.53** in good yield (84%) (Scheme **5-12**).


OH
OH
5.51
NaH/MeI
O
O
5.52 (79%)
HOAc/Br_2
Br
Br
O
O
5.53 (84)

Scheme 5-12

The functionalization of the dibromo species **5.53** was performed using a sequence of lithium-halogen exchanges and treatment with an appropriate electrophile. In the first case, after treating the dibromide **5.53** with one equivalent of *n*-butyl lithium, the anion formed was treated with dimethylsulfate to provide the desired monomethylated product **5.54** in good yield (95%). The crude reaction mixture was then treated with one equivalent of *n*-butyl lithium and then gaseous carbon dioxide was bubbled through the reaction mixture to provide the desired carboxylic acid **5.55** in good yield (77%) (Scheme **5-13**). This short and efficient sequence provided intermediate **5.55** in an overall yield of 49% from commercial resorcinol in four steps.



Scheme 5-13

This compound **5.55** is the furthest point reached in the synthesis of the desired intermediate **5.13**. From this point, future work remaining will involve the transformation of **5.55** into **5.21** using directed *ortho*-metallation chemistry to introduce functional groups that can be further manipulated to access the required aldehyde functionality needed for the second application of our allylboration methodology as proposed in Figure **5-6**. This could also be achieved through the same sequence employed in the synthesis of De Brabander and co-workers[9] (Scheme **5.2**).

5.3 Conclusion

Although the synthesis of psymberin is yet to be completed, some key progress and achievements have been accomplished. Importantly, it was proven that it is possible to apply the methodologies developed in our group, namely the Lewis acid-catalyzed allylboration of aldehydes and the tandem inverse-electron-demand-hetero-Diels-Alder/allylboration reaction, to the synthesis of key fragments of psymberin. The application of our Lewis acid-catalyzed aldehyde allylboration to the synthesis of fragment **5.11** in a fashion that equals and even surpasses the Brown allylation method used in De Brabander synthesis is remarkable. The intermediates **5.43** and **5.48** containing the complex pyran ring were successfully obtained through the tandem inverse-electron-demand-hetero-Diels-Alder/allylboration approach. This allowed for the rapid formation of a complex intermediate that can quickly be functionalized to the desired fragment **5.12**. The second application of our allylboration methodology could not be tested since the preparation of required aldehyde **5.21** was not completed. In this regard, an efficient route to an advanced intermediate **5.22** has been developed. From this intermediate, based on results reported by De Brabander and co-workers,[9] it is reasonable to believe that it is possible to reach the desired aldehyde in only a few more steps. Once the preparation of all three key fragments (**5.11**, **5.12** and **5.13**) has been completed, all that remains is the connection of the synthons with each other. This highly convergent approach will be attempted as described in our plan (Figure **5.3**), through the alkylation of the acetal and the Curtius rearrangement.

5.4 Experimental

5.4.1 General

The methods described in Section 2.7.1 also apply here.

5.4.2 Experimental procedures

D-(*R*)-glyceraldehyde acetonide (5.4)

This compound is known and was prepared according to the literature procedure.[18] This compound was stored and used as a 0.27 M solution in CH_2Cl_2.

(1'*R*,2*S*,6*R*)-(6-Ethoxy-5,5-dimethyl-5,6-dihydro-2*H*-pyran-2-yl)-hydroxy-acetic acid ethyl ester (5.16)

A mixture of 3-boronoacrolein pinacolate (**5.18**) (0.360 g, 2.00 mmol, 1.0 equiv) and 1-ethoxy-2-methyl-propene (**5.19**) (0.400 g, 4.00 mmol, 2.0 equiv) was placed in a flame dried round bottom flask equipped with a stirbar. To this solution was added **5.34** (49 mg, 0.10 mmol, 0.1 equiv) and powdered BaO (600 mg, 4 mmol, 2.0 equiv). After being stirred for 18 h at room temperature, the reaction mixture was diluted with ether (10 mL), and filtered through a short column (silica-gel deactivated with Et_3N, pentane/ether 4:1) to remove the catalyst.

A mixture of hetero-Diels-Alder cycloadduct **5.37** and ethyl glyoxalate (**5.17**) (0.80 mL, 4.00 mmol, 2.0 equiv), as a 50% solution in toluene, was stirred at 60 °C for 6 h in a sealed pressure tube. After being cooled to ambient temperature, a saturated aqueous solution of $NaHCO_3$ (2 mL) was added to the reaction mixture, which was stirred for 30 minutes. The resulting mixture was extracted with ether (2 × 10 mL). The ethereal layers were combined, washed with brine (10 mL), then dried over anhydrous sodium sulfate. After filtration and concentration *in vacuo* to evaporate ether, the residue was purified by flash column chromatography (silica-gel deactivated with Et_3N, pentane/ether 4:1) to afford **5.16** (0.258 g, 50%).

$[\alpha]^{23}_{D}$ –33.70 (c = 2.5, $CHCl_3$);

IR (neat, film, cm^{-1}) 3502, 2977, 1750;

^1H NMR (300 MHz, $CDCl_3$) δ 5.69 (dd, *J* = 10.2, 2.4 Hz, 1H), 5.54 (dd, *J* = 10.2, 1.8 Hz, 1H), 4.68 (dd, *J* = 2.3, 2,0 Hz, 1H), 4.34 (s, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 4.15 (dd, *J* = 9.7, 2.7 Hz, 1H), 3.90 (dddd, *J* = 16.9, 9.8, 9.8, 7.1 Hz, 1H), 3.61 (d, *J* = 9.7 Hz, 1H), 3.50 (dddd, *J* = 16.9, 9.8, 7.1, 7.1 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.02 (s, 3H), 1.00 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 136.9, 122.4, 104.2, 75.2, 72.8, 65.3, 61.4, 35.2, 25.7, 22.3, 14.4, 14.2;

HRMS (ESI, *m/z*) calcd for $C_{13}H_{22}O_5Na$ 281.1359, found 281.1359.

HPLC: performed on the phenylcarbamate derivative, Chiralcel AD-RH, 50% H_2O/isopropanol, 0.40 mL/min., UV detection at 210 nm, minor peak at 53.7 min., major peak at 59.5 min., 84% ee.

(*E*)-3-Boronoacrolein pinacol ester (5.18)

This compound is known and was prepared according to the literature procedure.[10]

1-Ethoxy-2-methyl-propene (5.19)

This compound is known[16,17] and was prepared according to the following procedure.

In a dry round bottom flask, isovaleraldehyde (25 mL, 274 mmol, 1.0 equiv) was charged. Triethylorthoformate (68 mL, 411 mmol, 1.5 equiv) was added followed by sulfamic acid (2.66 g, 27 mmol, 0.1 equiv). The reaction mixture was stirred at room temperature for 18 h. The flask was then equipped with a vigreux distillation column, a head thermometer, a condenser, and a collecting flask. The reaction mixture was heated to 95 °C for 2 h during which ethyl formate (Bp: 52-54 °C) was collected. The flask was then heated to 135 °C for 4 h during which ethanol and product **5.19** were collected over anhydrous K_2CO_3. The collected liquid was then extracted 3 times with a 1% aqueous solution of K_2CO_3. The leftover organic phase was dried using anhydrous K_2CO_3. This organic layer was redistilled using a vigreux column, the fraction collected over K_2CO_3 between 85-95 °C contained the pure compound **5.19** as clear colorless liquid (16 g, 60%). This product was stored over K_2CO_3 in the freezer for a few weeks.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (s, 1H), 3.72 (q, $J = 7.0$ Hz, 2H), 1.61 (s, 3H), 1.55 (s, 3H), 1.24 (t, $J = 7.0$ Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 139.8, 110.3, 67.1, 19.5, 15.3, 15.0.

(1*S*,2*R*,3*S*,4*R*)-2,3-O-[2-Methylallylboryl]-2-phenyl-1,7,7-trimethylbornanediol (5.23)

The enantiomer of this compound is known and was prepared according to the literature procedure[12,13] (see compound **2.2a** in this thesis).

(4*S*,5*R*)-5,6-O-Isopropylidene-2-methyl-hexene-4-ol (5.24)

This compound is known[9] and was prepared according to the literature procedure, [12,13] with two modifications; two equivalents of aldehyde were used and the reaction was left at –78 °C for 36 h instead of 18 h

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.89 (s, 1H), 4.82 (s, 1H), 4.05-3.93 (m, 3H), 3.90-3.83 (m, 1H), 2.30 (dd, *J* = 4.0, 14.2 Hz, 1H), 2.11 (dd, *J* = 9.4, 14.2 Hz, 1H), 2.01 (d, *J* = 2.4 Hz, 1H), 1.78 (s, 3H), 1.44 (s, 3H),1.37 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 141.9, 113.7, 109.1, 78.4, 68.8, 65.4, 41.7, 26.6, 25.3, 22.3.

(4*S*,5*R*)-5,6-O-Isopropylidene-4-methoxy-2-methyl-hexene (5.25)

This compound is known and was prepared according to the literature procedure.[9]

(*E*)-3-Boronoacrolein (5.29)

This compound is known and was prepared according to the literature procedure.[21]

(2*R*,4*R*)-2-Ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydro-*2H*-pyran (5.35)

The enantiomer of this compound is known and was prepared according to the literature procedure.[10] This compound was not isolated.

(2*R*,4*R*)-2-Ethoxy-4-hydroxy-3,4-dihydro-2*H*-pyran (5.36)

The enantiomer of this compound is known and was prepared according to the literature procedure.[10]

HPLC: Chiralcel AD-RH, 40% *i*-PrOH/H_2O, 0.30 mL/min., UV detection at 210 nm, minor peak at 10.0 min., major peak at 13.1 min., 95% ee.

(2*R*,4*S*)-2-Ethoxy-3,3-dimethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,4-dihydro-2*H*-pyran (5.37)

This compound was prepared according to the first step in the preparation of **5.16**. It was not isolated. The product is observed by ^{1}H NMR in the crude reaction mixture.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.25 (dd, *J* = 6.1, 2.5 Hz, 1H), 4.71 (dd, *J* = 6.1, 3.0 Hz, 1H), 4.38 (s, 1H), 3.89 (dddd, *J* = 14.2, 9.9, 7.2, 7.2 Hz, 1H), 3.54 (dddd, *J* = 14.2, 9.9, 7.0, 7.0 Hz, 1H), [illegible].62-1.58 (m, 1H), 1.26 (br s, 6H), 1.25 (br s, 6H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.07 (s, 3H), 0.99 (s, 3H).

(2*R*,4*S*)-2-Ethoxy-3,3-dimethyl-3,4-dihydro-2*H*-pyran-4-ol (5.38)

The crude Diels-Alder cycloadduct **5.37** was dissolved in THF (10 mL) and cooled to 0 °C. A 3 M aqueous solution of NaOAc (1.00 mL, 3.00 mmol) was added dropwise and the temperature maintained below 5 °C. Hydrogen peroxide (0.610 mL, 6.55 mmol) was added and the mixture was stirred at 0 °C for 1 hour. Water (10 mL) was then added and the aqueous layer extracted with ether (2 × 30 mL). The ether layers were combined, washed with an aqueous saturated solutions of NH_4Cl (15 mL) and NaCl (15 mL), then dried over anhydrous $MgSO_4$. Filtration and concentration *in vacuo* gave the crude product **5.29**, which was purified by flash column chromatography (silica-gel deactivated with Et_3N), pentane/ether 4:1) to provide **5.38** (100 mg, 30%) as a volatile clear oil.

IR (CH_2Cl_2, cast, cm^{-1}) 3559, 3446, 1651;

^1H NMR (300 MHz, $CDCl_3$) δ 6.14 (d, *J* = 6.1 Hz, 1H), 5.10 (dd, *J* = 6.1, 5.3 Hz, 1H), 4.61 (d, *J* = 1.4 Hz, 1H), 3.79 (dddd, *J* = 14.1, 9.7, 7.1, 7.1 Hz, 1H), 3.48 (dddd, *J* = 14.1, 9.7, 7.1, 7.1 Hz, 1H), 3.37 (br s, 1H), 2.78 (d, *J* = 9.2 Hz, 1H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.18 (s, 3H), 0.96 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 105.3, 104.3, 68.5, 64.6, 37.6, 23.6, 20.5, 15.1;

HRMS (EI, *m/z*) calcd for $C_9H_{16}O_3Na$ 195.0992, found 195.0992.

HPLC: Chiralcel AD-RH, 50% *i*-PrOH/H_2O, 0.30 mL/min., UV detection at 210 nm, minor peak at 12.5 min., major peak at 19.9 min., 84% ee.

(2*R*,3*S*,4*S*)2-Ethoxy-3-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,4-dihydro-2*H*-pyran (5.40)

The enantiomer of this compound is known and was prepared according to the literature procedure.[19] It was used crude in the next step.

(1'*R*,2*S*,5*S*,6*R*)-(6-Ethoxy-5-methyl-5,6-dihydro-2*H*-pyran-2-yl)-hydroxy-acetic acid ethyl ester (5.41)

This compound was prepared according to the preparation of **5.16**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddd, *J* = 10.2, 2.6, 2.3 Hz, 1H), 5.63 (ddd, *J* = 10.2, 2.2, 2.2 Hz, 1H), 4.75-4.72 (m, 1H), 4.67 (d, *J* = 3.8 Hz, 1H), 4.26 (dq, *J* = 7,8, 0.7 Hz, 2 H), 4.15 (dd, *J* = 10.0, 2.6 Hz, 1H) 3.93 (dddd, *J* = 14.1, 9.6, 7.1, 7.1 Hz, 1H) 3.84 (d, *J* = 10.0 Hz, 1H), 3.50 (dddd, *J* = 14.1, 9.6, 7.1, 7.1 Hz, 1H), 2.41-2.33 (m, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.03 (d, *J* = 7.2 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 131.2, 123.9, 99.1, 75.0, 73.0, 65.4, 61.3, 32.8, 25.1, 14.9, 14.5;

HRMS (EI, *m/z*) calcd for $C_{12}H_{18}O_4$ (M –H_2O) 226.1205, found 226.1208.

(1'*R*,2*S*,6*R*)-(6-Ethoxy-5,5-dimethyl-5,6-dihydro-2*H*-pyran-2-yl)-triisopropylsilanyloxy-acetic acid ethyl ester (5.42)

Imidazole (40 mg, 0.59 mmol, 1.5 equiv) and DMAP (5 mg, 0.06 mmol, 0.1 equiv) were added to a flame dried round bottom flask equipped with a stirbar. To these solids was added **5.16** (100 mg, 0.39 mmol, 1.0 equiv) in dichloromethane (2 mL). The mixture was cooled to 0 °C and triisopropylsilane trifluoromethanesulfonate (150 μL, 0.59 mmol, 1.5 equiv) was added dropwise.

The reaction mixture was warmed up to room temperature and stirred for 18 h. A saturated aqueous ammonium chloride solution (5 mL) was added to the reaction mixture and stirred for 15 minutes. The mixture was extracted three times with ether, the combined organic layers were washed once with water and once with brine. The ether layer was then dried over anhydrous sodium sulfate, filtered, and the solvent was removed in vacuo. The crude mixture was purified by flash column chromatography (silica-gel deactivated with Et_3N, pentane/ether 4:1) to provide **5.42** (117 mg, 72%) as a clear oil.

$[\alpha]^{23}_{D}$ –49.79 (c = 2.7, $CHCl_3$);

IR (neat, film, cm^{-1}), 2944, 2868, 1751;

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.61 (dd, *J* = 10.0, 1.3 Hz, 1H), 5.54 (dd, *J* = 10.0, 2.0 Hz, 1H), 4.44 (s, 1H), 4.40 (ddd, *J* = 5.3, 2,2, 1.5 Hz, 1H), 4.24 (s, 1H), 4.24-4.12 (m, 2H), 3.91 (dddd, *J* = 16.9, 9.9, 7.1, 7.1, Hz, 1H), 3.50 (dddd, *J* = 16.9, 9.8, 7.1, 7.1 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H), 1.13-1.05 (m, 21H), 0.96 (s, 3H), 0.94 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 137.4, 122.6, 105.2, 77.7, 74.7, 64.5, 60.6, 36.0, 24.3, 21.0, 17.8, 15.1, 14.2, 12.2;

HRMS (ESI, *m/z*) calcd for $C_{22}H_{42}O_5SiNa$ 437.2692, found 437.2694.

(1'*R*,2*S*,5*S*)-(4-Ethoxy-5,5-dimethyl-3,7-dioxa-bicyclo[4.1.0]hept-2-yl)-hydroxy-acetic acid ethyl ester (5.43)

In a dry round bottom flask equipped with a stirbar was added a solution of **5.16** (129 mg, 0.5 mmol, 1.0 equiv) in dichloromethane (2 mL). *m*-CPBA <77% (135 mg, 0.6 mmol, 1.2 equiv) was added in one portion to the solution and was stirred for four days at room temperature. A saturated aqueous solution of sodium bicarbonate (5 mL) was added to the crude reaction mixture. The reaction was then extracted three times using dichloromethane, the organic layers were combined and washed once with water and once with brine. The dichloromethane layers were then dried over anhydrous sodium sulfate, filtered, and solvent removed in vacuo. The product was then purified by flash column chromatography (silica-gel deactivated with Et_3N, pentane/ether 3:2) to provide **5.43** (48 mg, 35%) as a white solid.

Mp: 56-58 °C (uncorrected)

$[\alpha]^{23}$[illegible] –51.81 (c = 2.8, $CHCl_3$);

IR (neat, film, cm^{-1}) 3477, 2977, 2933, 2874, 1748;

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.39 (dd, *J* = 8.8, 2.2 Hz, 1H), 4.35-4.22 (m, 3H), 4.21 (s, 1H), 3.68 (dddd, *J* = 14.2, 9.2, 7.1, 7.1 Hz, 1H), 3.38 (dddd, *J* = 14.2, 9.8, 7.1, 7.1 Hz, 1H), 3.36 (d, *J* = 7.0 Hz, 1H), 3.14 (d, *J* = 8.8 Hz, 1H), 3.02 (dd, *J* = 4.1, 0.6 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H), 1.10 (s, 3H), 1.04 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 101.6, 75.4, 72.1, 65.1, 62.1, 61.8, 54.0, 34.8, 21.1, 16.5, 14.9, 14.1;

HRMS (ESI, *m/z*) calcd for $C_{13}H_{22}O_6Na$ 297.1307, found 297.1309.

(1'*R*,2*S*,4*R*,5*S*)-(4-Ethoxy-5-methyl-3,7-dioxa-bicyclo[4.1.0]hept-2-yl)-hydroxy-acetic acid ethyl ester (5.48)

In a round bottom flask open to air equipped with a stirbar was added **5.41** (50 mg, 0.20 mmol, 1.0 equiv) and sodium bicarbonate (76 mg, 0.50 mmol, 4.5 equiv) in H_2O (0.5 mL) and acetone (1 mL). The mixture was stirred at room temperature and Oxone® (184 mg, 0.30 mmol, 1.5 equiv) was added slowly. The resulting mixture was stirred at room temperature for two hours. The reaction was then extracted three times with ethyl acetate and the combined organic layers were washed once with a saturated solution of $Na_2S_2O_5$, once with water, and once with brine. The resulting ethyl acetate layer was dried using anhydrous sodium sulfate, filtered, and the solvent was removed in vacuo. The product was then purified by flash column chromatography (silica-gel deactivated with Et_3N, pentane/ether 3:2) to provide **5.48** (43 mg, 81%) as a clear colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.55 (d, *J* = 2.9 Hz, 1H), 4.40-4.36 (m, 2H), 4.28 (dddd, *J* = 10.8, 10.8, 2.6, 2.6 Hz, 2H), 3.73 (dddd, *J* = 14.2, 9.6, 7.1, 7.1 Hz, 1H), 3.40 (dddd, *J* = 14.2, 9.6, 7.1, 7.1 Hz, 1H), 3.31 (d, *J* = 1.0 Hz, 1H), 3.29 (d, *J* = 6.8 Hz, 1H) 3.25 (ddd, *J* = 4.1, 1.9, 0.2 Hz, 1H), 2.27 (dddd, *J* = 11.7, 4.8, 2.1, 2.1 Hz, 1H), 1.31 (t, $J = 7.1$ Hz, 3H), 1.17 (t, $J = 6.1$ Hz, 3H), 1.07 (d, $J = 7.1$ Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 131.1, 75.3, 72.4, 65.2, 61.9, 57.6, 52.0, 33.0, 15.1, 14.3, 9.1;

HRMS (EI, *m/z*) calcd for $C_{12}H_{19}O_6$ (M –H) 259.1182, found 259.1193.

1,3-Dimethoxy-benzene (5.52)

This compound is known[22] and was prepared according to the following procedure.

Sodium hydride 60% in mineral oil (1.10 g, 42 mmol, 2.1 equiv) was introduced in a flame dried round bottom flask. The solid was placed under vacuum (<1 mm Hg) and the flask was filled with N_2. Under an inert atmosphere THF (50 mL) was added to the solid and cooled to 0 °C. Resorcinol (2.20 g, 20 mmol, 1.0 equiv) was slowly added to the slurry as a solution in THF (50 mL). The resulting mixture was stirred at room temperature for two hours The reaction was cooled back to 0 °C and methyl iodide (2.8 mL, 44 mmol, 2.2 equiv) was slowly added and the reaction was stirred at room temperature for 16 h. The reaction mixture was poured slowly over an aqueous saturated ammonium chloride solution (100 mL) and stirred at room temperature for 15 minutes. The mixture was extracted three times with ether, the organic layers were combined, washed once with water, once with brine, dried over anhydrous magnesium sulfate, filtered, and the solvent was removed in vacuo. The product was then purified by flash column chromatography (Ethyl acetate/hexane 3:7) to provide **5.52** (2.17 g, 79%) as a clear colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19-7.15 (m, 1H), 6.51-6.45 (m, 3H), 3.78 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 130.0, 106.3, 100.7, 55.2.

1,5-Dibromo-2,4-dimethoxy-benzene (5.53)

This compound is known[23] and was prepared according to the following procedure.

The compound **5.52** (1.85 g, 13.4 mmol, 1.0 equiv) was introduced in a flame dried round bottom flask. Acetic acid (2 mL) and bromine (163 μL, 3.2 mmol,

2.2 equiv) were added sequentially and stirred at room temperature for two hours. A saturated aqueous solution of $Na_2S_2O_3$ (5 mL) was added and stirred for 15 minutes. The mixture was extracted three times with ethyl acetate, the combined organic layers were washed twice with a saturated aqueous solution of $Na_2S_2O_3$, twice with a 1 M aqueous solution of sodium hydroxide, once with water, and once with brine. The ethyl acetate layer was dried over anhydrous magnesium sulfate, filtered, and the solvent removed in vacuo. The product was used without purification in the following step as an off-white powder (3.33 g, 84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 6.48 (s, 1H), 3.89 (s, 6H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 136.0, 102.5, 97.5, 56.6;

HRMS (EI, *m/z*) calcd for $C_8H_8{}^{79}Br{}^{81}BrO_2$ 295.8871 found 295.8873.

1-Bromo-2,4-dimethoxy-5-methyl-benzene (5.54)

This compound is known[24] and was prepared according to the following procedure.

In a flame dried round bottom flask was charged dibromide **5.53** (600 mg, 2.0 mmol, 1 equiv) and dissolved in ether (30 mL). To the stirred solution, a solution of *n*-BuLi (1.55 M in hexane, 1.31 mL, 2.0 mmol, 1.0 equiv) was added at room temperature and stirred for 15 minutes. The reaction mixture was then cooled to 0 °C and dimethylsulfate (0.30 mL, 3.1 mmol, 1.5 equiv) was added dropwise. The resulting mixture was stirred at room temperature for one hour. Water was added to the reaction mixture and stirred for 15 minutes followed by extraction with ether three times. The combined organic layers were washed once with water and once with brine. The ether phase was dried over anhydrous magnesium sulfate, filtered, and the solvent was removed in vacuo to afford the product as a white powder (443 mg, 95%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (s, 1H), 6.45 (s, 1H), 3.88 (s 3H), 3.83 (s, 3H), 2.12 (s, 3H);

HRMS (EI, *m/z*) calcd for $C_9H_{11}{}^{79}BrO_2$ 229.9943 found 229.9946.

2,4-Dimethoxy-5-methyl-benzoic acid (5.55)

This compound is known[9] and was prepared according to the following procedure.

In a flame dried round bottom flask was charged bromide **5.54** (274 mg, 1.20 mmol, 1.0 equiv) and dissolved in ether (10 mL). To the stirred solution, a solution of *n*-BuLi (1.55 M in hexane, 0.81 mL, 1.25 mmol, 1.05 equiv) was added at room temperature and stirred for 15 minutes. The reaction mixture was then cooled to 0 °C and carbon dioxide (sublimed dry ice) was bubbled through the solution via a canula. The resulting mixture was stirred at room temperature for 30 minutes. Water was added to the reaction mixture. The pH of the mixture was acidify using a 1 M aqueous HCl solution (pH <2) and stirred for 15 minutes followed by extraction with ether three times. The combined organic layers were washed once with water and once with brine. The ether phase was dried over anhydrous magnesium sulfate, filtered, and the solvent was removed in vacuo to afford the product as an off-white powder (180 mg, 77%).

^{1}H NMR ($CDCl_3$) δ 10.61 (br s,1H), 7.91 (d, J = 0.8 Hz, 1H), 6.46 (s, 1H), 4.07 (s, 3H), 3.92 (s, 3H), 2.16 (s, 3H);

^{13}C NMR ($CDCl_3$) δ 165.6, 162.9, 158.2, 134.7, 120.6, 108.8, 94.1, 56.7, 55.6, 15.1.

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Chapter 6

Thesis Conclusions

This thesis describes research related to the Lewis acid-catalyzed enantioselective aldehyde allylboration discovered in the Hall laboratory in 2002. During the course of this work, many notable milestones have been reached. This includes the development and optimization of a reliable, efficient, operationally simple, and general $Sc(OTf)_3$-catalyzed enantioselective allylboration of aldehydes. Because this method requires the use of a chiral diol derived from camphor, a new and improved synthesis of this chiral auxiliary was also developed. This catalytic manifold was applied to the addition of α-substituted allylic boronates to aldehydes. This newly developed methodology, in conjunction with another methodology developed in the Hall laboratory by Xuri Gao, namely the tandem inverse-electron-demand-hetero-Diels-Alder/allylboration reaction, was applied to the synthesis of an intermediate for the complex natural product psymberin.

The success of the Lewis acid-catalyzed allylboration of aldehydes was remarkable since it constituted the first report of simple allylic boronate species affording enantioselectivities consistently above 90%. The optimal camphor-derived chiral auxiliary used in conjunction with the newly developed catalytic manifold allowed for the preparation of a wide range of homoallylic alcohols. These could be derived from a large variety of substrates including aromatic, aliphatic, propargylic, and secondary aldehydes. Even functionalized aldehydes were successfully used with this new method. Although this method makes use of one equivalent of the complex chiral diol, we have demonstrated the possibility to recover the chiral auxiliary almost quantitatively. We also used these new reaction conditions in the preparation of over one gram of homoallylic alcohol with results reflecting those obtained in the smaller scale studies. The simultaneous extension of this methodology by Dr. Michel Gravel and Dr. Xiaosong Lu to the *E* and *Z*-crotylation using the same reaction conditions was also a reflection of the generality and ease of operation of this reaction.

During the course of our investigations into the Lewis acid-catalyzed allylboration of aldehydes, we found that the diol providing the best enantioselectivity and the best yields was the diol derived from camphor. To render this method more accessible to the organic chemistry community, an improved preparation of this diol was considered necessary. We have been able, through the use of simple and easily accessible reagents, to develop two new syntheses of this diol. In our first approach, the desired diol was obtained in two steps from commercially available camphorquinone. This first synthesis was achieved through careful reduction of the least hindered diol using L-Selectride followed by addition of the phenyl cerium reagent to the remaining ketone. In this step, the use of the cerium reagent was crucial since all other reagents, such as Grignard reagents or phenyl lithium, led to poor yields. This sequence afforded the desired diol in 55% yield with a simple final recrystallization after the final step. The second successful approach started from simple camphor and provided us with the desired diol in four steps and an overall yield of 55%. This was achieved by first forming the triethylsilyl enol ether of camphor followed by its oxidation by DMDO. The newly formed alkoxyketone was reacted using the same phenyl cerium as in the previous synthesis. The obtained addition product was then treated with acetic acid, water, and THF to generate, after recrystallization, the desired camphor-derived diol. These two newly developed syntheses, which significantly improve upon the previous literature preparation, should promote the use of our $Sc(OTf)_3$ catalyzed allylboration reaction of aldehyde by other research groups.

During the exploration of potential applications of the Lewis acid-catalyzed allylboration reaction to other classes of allylboration reagents, we considered its application in the context of α-silyl substituted allylic boronates. This study demonstrated how thin is the mechanistic line between boronate activation and aldehyde activation. The thermal addition reactions provided the expected allylboration product with similar *E*:*Z* ratio as those reported in the literature. In the case where catalysis was used with the pinacol boronate reagents, both Lewis acids and Brønsted acids afforded the allylsilation product as the major species. When the bulkier camphor-derived auxiliary was used, the yields of all the reactions were very low. When $Sc(OTf)_3$ is used as the catalyst, some of the allylboration product can be observed but only with marginal yield (20%) and enantioselectivity (60%). Interestingly, when triflic acid was used, the major product observed was the allylsilation product with the presence of many side reaction products. Thus, this Lewis acid-catalyzed manifold cannot reliably be used in the case of α-silyl substituted allylic boronates.

To ascertain our methodology as a new tool for organic chemists, we investigated its application towards the synthesis of the natural anticancer agent psymberin. In the course of this application, we used our camphor-derived methallyl reagent and reacted it under the catalytic conditions with D-(*R*)-glyceraldehyde acetonide to provide the desired intermediate in 75% yield as a single diastereoisomer. This intermediate can further be transformed into the requisite carboxylic acid for the synthesis of the aminal side chain of psymberin. To access the pyran core, the tandem IEDHDA/allylboration reaction was applied to borono acrolein pinacolate, ethyl 2-methylpropenyl ether, and ethyl glyoxalate to generate the complex pyran in good overall yield (50%). This dihydropyran intermediate was then epoxidized to introduce the future hydroxyl group on carbon C11. Significant progress was also achieved on the synthesis of the aromatic side chain. In this case, an advanced intermediate toward the aldehyde required for the second application of our Lewis acid-catalyzed *Z*-crotylation was obtained. Although a lot of work is still needed for the completion of psymberin, significant progress has been achieved. Once the final steps are finalized, this convergent approach towards psymberin will allow for the quick and efficient preparation of analogues, which in turn will be tested for their anticancer activity. Efforts to complete the total synthesis of psymberin are currently underway in the Hall laboratory.

Overall, the main contribution of this thesis is highlighted in the development of the enantioselective Lewis acid-catalyzed allylboration of aldehydes. This method was demonstrated to be very general, both in terms of aldehyde and allylic reagents. It also provided consistently good enantio- and diastereoselectivities. This method was rendered more accessible to the organic chemistry community through the successful development of two improved syntheses of the required chiral auxiliary. The application of this new catalytic manifold to the preparation of a key intermediate towards the synthesis of the anticancer agent psymberin is remarkable. The preparation of the key pyran core of psymberin using the tandem IEDHD/allylboration reaction with a trisubstituted enol ether pushes further the limits of this powerful reaction.